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(54) Title: CYTOKINE-, STRESS-, AND ONCOPROTEIN-ACTIVATED HUMAN PROTEIN KINASE KINASES		
(57) Abstract <p>Disclosed are human mitogen-activated (MAP) kinase kinase isoforms (MKKs). MKKs mediate unique signal transduction pathways that activate human MAP kinases p38 and JNK, which result in activation of other factors, including activating transcription factor-2 (ATF2) and c-Jun. The pathways are activated by a number of factors, including cytokines and environmental stress. Methods are provided for identifying reagents that modulate MKK function or activity and for the use of such reagents in the treatment of MKK-mediated disorders.</p> <div data-bbox="812 1134 1396 1932"> <pre> graph LR MKK1 --- Node1 MKK2 --- Node1 Node1 --- Node2 Node2 --- MKK7 Node2 --- Node3 Node3 --- HEP Node3 --- Node4 Node4 --- MKK4 Node4 --- Node5 Node5 --- MKK3 Node5 --- Node6 Node6 --- MKK6 Node6 --- MKK5 </pre> </div>		

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CYTOKINE-, STRESS-, AND ONCOPROTEIN-ACTIVATED HUMAN
PROTEIN KINASE KINASES

5 Background of the Invention

This invention relates to protein kinases.

Mitogen-activated protein (MAP) kinases are important mediators of signal transduction from the cell surface to the nucleus. Multiple MAP kinases have been
10 described in yeast including SMK1, HOG1, MPK1, FUS3, and KSS1. In mammals, the MAP kinases identified are extracellular signal-regulated MAP kinase (ERK), c-Jun amino-terminal kinase (JNK), and p38 kinase (Davis (1994) Trends Biochem. Sci. 19:470). These MAP kinase isoforms
15 are activated by dual phosphorylation on threonine and tyrosine.

Activating Transcription Factor-2 (ATF2), ATF α , and cAMP Response Element Binding Protein (CRE-BP α) are related transcription factors that bind to similar
20 sequences located in the promoters of many genes (Ziff (1990) Trends in Genet. 6:69). The binding of these transcription factors leads to increased transcriptional activity. ATF2 binds to several viral proteins, including the oncoprotein Ela (Liu and Green (1994)
25 Nature 368:520), the hepatitis B virus X protein (Maguire et al. (1991) Science 252:842), and the human T cell leukemia virus 1 tax protein (Wagner and Green (1993) Science 262:395). ATF2 also interacts with the tumor suppressor gene product Rb (Kim et al. (1992) Nature
30 358:331), the high mobility group protein HMG(I)Y (Du et al. (1993) Cell 74:887), and the transcription factors nuclear NF- κ B (Du et al. (1993) Cell 74:887) and c-Jun (Benbrook and Jones (1990) Oncogene 5:295).

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Summary of the Invention

The invention is based on the identification and isolation of a new group of human mitogen-activated protein kinase kinases (MKKs). The MKK isoforms described herein, MKK3, MKK6, MKK4 (including MKK4- α , - β , and - γ), MKK7 (including murine MKK7, human MKK7, MKK7b, MKK7c, MKK7d, and MKK7e) have serine, threonine, and tyrosine kinase activity. MKK3, MKK4, and MKK6 specifically phosphorylate the human MAP kinase p38 at Thr¹⁸⁰ and Tyr¹⁸². The MKK4 isoforms also phosphorylate the human MAP kinases JNK (including JNK1, JNK2, and JNK5) at Thr¹⁸³ and Tyr¹⁸⁵. The MKK7 isoforms phosphorylate JNK at Thr¹⁸³ and Tyr¹⁸⁵.

Accordingly, the invention features a substantially pure human MKK polypeptide having serine, threonine, and tyrosine kinase activity that specifically phosphorylates human p38 MAP kinase. MKK3 has the amino acid sequence of SEQ ID NO:2. The invention further includes MKK6 having the amino acid sequence of SEQ ID NO:4 and having serine, threonine, and tyrosine kinase activity that specifically phosphorylates human p38 MAP kinase.

The invention further features a substantially pure human MKK polypeptide having serine, threonine, and tyrosine kinase activity that specifically phosphorylates human p38 MAP kinase and JNK. MKK4 isoform MKK4- α has the amino acid sequence of SEQ ID NO:6. MKK4 isoform MKK4- β has the amino acid sequence of SEQ ID NO:8. MKK4 isoform MKK4- γ has the amino acid sequence of SEQ ID NO:10.

The invention also features a substantially pure MKK polypeptide (MKK7) having serine, threonine, and tyrosine kinase activity that specifically phosphorylates mitogen-activated protein kinase JNK. MKK isoforms MKK7 (murine) and MKK7 (human) have the amino acid sequences

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of SEQ ID NOS:18 and 26, respectively. The MKK7 isoforms MKK7b, MKK7c, MKK7d, and MKK7e have the amino acid sequences of SEQ ID NO:20, SEQ ID NO:28, SEQ ID NO:30, and SEQ ID NO:32, respectively.

5 As used herein, the term "mitogen-activating protein kinase kinase" or "MKK" means a protein kinase which possesses the characteristic activity of phosphorylating and activating a human mitogen-activating protein kinase. Examples of MKKs include MKK3 and
10 MKK6, which specifically phosphorylate and activate p38 MAP kinase at Thr¹⁸⁰ and Tyr¹⁸², MKK4 isoforms which specifically phosphorylate and activate p38 MAP kinase at Thr¹⁸⁰ and Tyr¹⁸², and JNK at Thr¹⁸³ and Tyr¹⁸⁵, and MKK7 isoforms which specifically phosphorylate JNK at Thr¹⁸³
15 and Tyr¹⁸⁵.

An "MKK7" is a mammalian isoform of mitogen-activated protein kinase kinase (MKK) polypeptide having serine, threonine, and tyrosine kinase activity, and phosphorylating mitogen-activated protein (MAP) kinase
20 JNK but not p38.

The invention includes the specific p38 and JNK MKKs disclosed, as well as closely related MKKs which are identified and isolated by the use of probes or antibodies prepared from the polynucleotide and amino
25 acid sequences disclosed for the MKKs of the invention. This can be done using standard techniques, e.g., by screening a genomic, cDNA, or combinatorial chemical library with a probe having all or a part of the nucleic acid sequences of the disclosed MKKs. The invention
30 further includes synthetic polynucleotides having all or part of the amino acid sequence of the MKKs herein described.

The term "polypeptide" means any chain of amino acids, regardless of length or post-translational
35 modification (e.g., glycosylation or phosphorylation),

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and includes natural proteins as well as synthetic or recombinant polypeptides and peptides.

The term "substantially pure," when referring to a polypeptide, means a polypeptide that is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. A substantially pure MKK polypeptide (e.g., human) is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, MKK polypeptide. A substantially pure MKK can be obtained, for example, by extraction from a natural source; by expression of a recombinant nucleic acid encoding a MKK polypeptide, or by chemically synthesizing the protein. Purity can be measured by any appropriate method, e.g., column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

In one aspect, the invention features isolated polynucleotides which encode the MKKs of the invention. In one embodiment, the polynucleotide is the nucleotide sequence of SEQ ID NO:1. In other embodiments, the polynucleotide is the nucleotide sequence of SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, or SEQ ID NO:31, respectively.

As used herein, "polynucleotide" refers to a nucleic acid sequence of deoxyribonucleotides or ribonucleotides in the form of a separate fragment or a component of a larger construct. DNA encoding portions or all of the polypeptides of the invention can be assembled from cDNA fragments or from oligonucleotides that provide a synthetic gene which can be expressed in a recombinant transcriptional unit. Polynucleotide sequences of the invention include DNA, RNA, and cDNA sequences, and can be derived from natural sources or

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synthetic sequences synthesized by methods known to the art.

An "isolated" polynucleotide is a nucleic acid molecule that is separated in some way from sequences in the naturally occurring genome of an organism. Thus, the term "isolated polynucleotide" includes any nucleic acid molecules that are not naturally occurring. The term therefore includes, for example, a recombinant polynucleotide which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequences.

The isolated polynucleotide sequences of the invention also include polynucleotide sequences that hybridize under stringent conditions to the polynucleotide sequences specified herein. The term "stringent conditions" means hybridization conditions that guarantee specificity between hybridizing polynucleotide sequences, such as those described herein, or more stringent conditions. One skilled in the art can select posthybridization washing conditions, including temperature and salt concentrations, which reduce the number of nonspecific hybridizations such that only highly complementary sequences are identified (Sambrook et al. (1989) in Molecular Cloning, 2d ed.; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY).

The isolated polynucleotide sequences of the invention also include sequences complementary to the polynucleotides encoding MKK (antisense sequences). Antisense nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule (Weintraub (1990) Scientific American 262:40). The invention includes all antisense polynucleotides that

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inhibit production of MKK polypeptides. In the cell, the antisense nucleic acids hybridize to the corresponding mRNA, forming a double-stranded molecule. Antisense oligomers of about 15 nucleotides are preferred, since they are easily synthesized and introduced into a target MKK-producing cell. The use of antisense methods to inhibit the translation of genes is known in the art, and is described, e.g., in Marcus-Sakura Anal. Biochem., 172:289 (1988).

10 In addition, ribozyme nucleotide sequences for MKK are included in the invention. Ribozymes are RNA molecules possessing the ability to specifically cleave other single-stranded RNA in a manner analogous to DNA restriction endonucleases. Through the modification of nucleotide sequences encoding these RNAs, molecules can be engineered to recognize specific nucleotide sequences in an RNA molecule and cleave it (Cech (1988) J. Amer. Med. Assn. 260:3030). A major advantage of this approach is that, because they are sequence-specific, only mRNAs with particular sequences are inactivated.

There are two basic types of ribozymes, tetrahymena-type (Hasselhoff (1988) Nature 334:535) and "hammerhead"-type. Tetrahymena-type ribozymes recognize sequences which are four bases in length, while "hammerhead"-type ribozymes recognize base sequences 11-18 bases in length. The longer the sequence, the greater the likelihood that the sequence will occur exclusively in the target mRNA species. Consequently, hammerhead-type ribozymes are preferable to tetrahymena-type ribozymes for inactivating a specific mRNA species, and 18-base recognition sequences are preferable to shorter recognition sequences.

The MKK polypeptides can also be used to produce antibodies that are immunoreactive or bind epitopes of the MKK polypeptides. Accordingly, one aspect of the

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invention features antibodies to the MKK polypeptides of the invention. The antibodies of the invention include polyclonal antibodies which include pooled monoclonal antibodies with different epitopic specificities, as well as distinct monoclonal antibody preparations. Monoclonal antibodies are made from antigen-containing fragments of the MKK polypeptide by methods known in the art (see, for example, Kohler et al. (1975) Nature 256:495).

The term "antibody" as used herein includes intact molecules as well as fragments thereof, such as F_a , $F(ab')_2$, and F_v , which are capable of binding an epitopic determinant. Antibodies that specifically bind MKK polypeptides can be prepared using intact polypeptides or fragments containing small peptides of interest as the immunizing antigen. The polypeptide or peptide used to immunize an animal can be derived from translated cDNA or chemically synthesized, and can be conjugated to a carrier protein, if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin and thyroglobulin. The coupled peptide is then used to immunize the animal (e.g., a mouse, a rat, or a rabbit).

A molecule (e.g., antibody) that "specifically binds" is one that binds to a particular polypeptide, e.g., MKK7, but that does not substantially recognize or bind to other molecules in a sample, e.g., a biological sample which includes MKK7. References to constructs made of an antibody (or fragment thereof) coupled to a compound comprising a detectable marker include constructs made by any technique, including chemical means and recombinant techniques.

The invention also features methods of identifying subjects at risk for MKK-mediated disorders by measuring activation of the MKK signal transduction pathway. Activation of the MKK signal transduction pathway can be

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determined by measuring MKK synthesis; activation of MKK isoforms; activation of MKK substrates p38 or JNK isoforms; or activation of p38 and JNK substrates such as ATF2, ATFa, CRE-BPa, and c-Jun. The term "JNK" or "JNK
5 isoforms" includes JNK1, JNK2, and JNK3. The term "MKK substrate" as used herein includes MKK substrates, as well as MKK substrate substrates, e.g., p38, JNK, ATF2, and c-Jun.

In one embodiment, activation of the MKK signal
10 transduction pathway is determined by measuring activation of the appropriate MKK signal transduction pathway substrates (for example, selected from p38, JNK isoforms, ATF2, ATFa, CRE-BPa, or c-Jun). MKK activity is measured by the rate of substrate phosphorylation as
15 determined by quantitation of the rate of labelled phosphorus (e.g., [³²]P or [³³]P) incorporation. This can also be measured using phosphorylation-specific reagents, such as antibodies. The specificity of MKK substrate phosphorylation can be tested by measuring p38
20 activation, JNK activation, or both, or by employing mutated p38 or JNK molecules that lack the sites for MKK phosphorylations. Altered phosphorylation of the substrate relative to control values indicates alteration of the MKK signal transduction pathway, and increased
25 risk in a subject of an MKK-mediated disorder. MKK activation of p38 and JNK can be detected in a coupled assay with the MKK signal transduction substrate ATF2, or related compounds such as ATFa and CRE-BPa. Activation can also be detected with the substrate c-Jun. When ATF2
30 is included in the assay, it is present as an intact protein or as a fragment of the intact protein, e.g., the activation domain (residues 1-109, or a portion thereof). ATF2 is incubated with a test sample in which MKK activity is to be measured and [γ -³²P]ATP, under
35 conditions sufficient to allow the phosphorylation of

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ATF2. ATF2 is then isolated and the amount of phosphorylation quantitated. In a specific embodiment, ATF2 is isolated by immunoprecipitation, resolved by SDS-PAGE, and detected by autoradiography.

5 In another embodiment, activation of the MKK signal transduction pathway is determined by measuring the level of MKK expression in a test sample. In a specific embodiment, the level of MKK expression is measured by Western blot analysis. The proteins present
10 in a sample are fractionated by gel electrophoresis, transferred to a membrane, and probed with labeled antibodies to MKK. In another specific embodiment, the level of MKK expression is measured by Northern blot analysis. Total cellular or polyadenylated [poly(A)*]
15 mRNA is isolated from a test sample. The RNA is fractionated by electrophoresis and transferred to a membrane. The membrane is probed with labeled MKK cDNA. In another embodiment, MKK expression is measured by quantitative PCR applied to expressed mRNA.

20 The MKKs of the invention are useful for screening reagents that modulate MKK activity. MKKs are activated by phosphorylation. Accordingly, in one aspect, the invention features methods for identifying a reagent which modulates MKK activity, by incubating MKK with the
25 test reagent and measuring the effect of the test reagent on MKK synthesis, phosphorylation, function, or activity. In one embodiment, the test reagent is incubated with MKK and [³²]P-ATP, and the rate of MKK phosphorylation determined, as described above. In another embodiment,
30 the test reagent is incubated with a cell transfected with an MKK polynucleotide expression vector, and the effect of the test reagent on MKK transcription is measured by Northern blot analysis, as described above. In a further embodiment, the effect of the test reagent
35 on MKK synthesis is measured by Western blot analysis

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using an antibody to MKK. In still another embodiment, the effect of a reagent on MKK activity is measured by incubating MKK with the test reagent, [³²]P-ATP, and a substrate in the MKK signal transduction pathway, including one or more of p38, JNK, and ATF2. The rate of substrate phosphorylation is determined as described above.

The term "modulation of MKK activity" includes inhibitory or stimulatory effects.

10 The invention is particularly useful for screening reagents that inhibit MKK activity. Such reagents are useful for the treatment or prevention of MKK-mediated disorders, for example, inflammation and oxidative damage.

15 The invention further features a method of treating a MKK-mediated disorder by administering to a subject in need thereof, an effective dose of a therapeutic reagent that inhibits the activity of MKK.

An "MKK-mediated disorder" is a pathological condition resulting, at least in part, from excessive activation of an MKK signal transduction pathway. The MKK signal transduction pathways are activated by several factors, including inflammation and stress. MKK-mediated disorders include, for example, ischemic heart disease, burns due to heat or radiation (UV, X-ray, γ , β , etc.), kidney failure, liver damage due to oxidative stress or alcohol, respiratory distress syndrome, septic shock, rheumatoid arthritis, autoimmune disorders, and other types of inflammatory diseases.

30 A "therapeutic reagent" any compound or molecule that achieves the desired effect on an MKK-mediated disorder when administered to a subject in need thereof.

MKK-mediated disorders further include proliferative disorders, particularly disorders that are

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stress-related. Examples of stress-related MKK-mediated proliferative disorders are psoriasis, acquired immune deficiency syndrome, malignancies of various tissues of the body, including malignancies of the skin, bone marrow, lung, liver, breast, gastrointestinal system, and genito-urinary tract. Preferably, therapeutic reagents inhibit the activity or expression of MKK inhibit cell growth or cause apoptosis.

A therapeutic reagent that "inhibits MKK activity" interferes with a MKK-mediated signal transduction pathway. For example, a therapeutic reagent can alter the protein kinase activity of MKK, decrease the level of MKK transcription or translation, e.g., an antisense polynucleotide able to bind MKK mRNA, or suppress MKK phosphorylation of p38, JNK, or ATF2, thus disrupting the MKK-mediated signal transduction pathway. Examples of such reagents include antibodies that bind specifically to MKK polypeptides, and fragments of MKK polypeptides that competitively inhibit MKK polypeptide activity.

A therapeutic reagent that "enhances MKK activity" supplements a MKK-mediated signal transduction pathway. Examples of such reagents include the MKK polypeptides themselves, which can be administered in instances where the MKK-mediated disorder is caused by under expression of the MKK polypeptide, or expression of a mutant MKK polypeptide. In addition, portions of DNA encoding an MKK polypeptide can be introduced into cells that under express an MKK polypeptide.

A "therapeutically effective amount" is an amount of a reagent sufficient to decrease or prevent the symptoms associated with the MKK-mediated disorder.

Therapeutic reagents for treatment of MKK-mediated disorders identified by the methods of the invention are administered to a subject in a number of ways known to the art, including parenterally by injection, infusion,

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sustained-release injection or implant, intravenously, intraperitoneally, intramuscularly, subcutaneously, or transdermally. Epidermal disorders and disorders of the epithelial tissues are treated by topical application of the reagent. The reagent is mixed with other compounds to improve stability and efficiency of delivery (e.g., liposomes, preservatives, or dimethyl sulfoxide (DMSO)). Polynucleotide sequences, including antisense sequences, can be therapeutically administered by techniques known to the art resulting in introduction into the cells of a subject suffering from the MKK-mediated disorder. These methods include the use of viral vectors (e.g., retrovirus, adenovirus, vaccinia virus, or herpes virus), colloid dispersions, and liposomes.

The materials of the invention are ideally suited for the preparation of a kit for the detection of the level or activity of MKK. Accordingly, the invention features a kit comprising an antibody that binds MKK, or a nucleic acid probe that hybridizes to a MKK polynucleotide, and suitable buffers. The probe or monoclonal antibody can be labeled to detect binding to a MKK polynucleotide or protein. In a preferred embodiment, the kit features a labeled antibody to MKK.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

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Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

Detailed Description

5 The drawings will first be described.

Drawings

Fig. 1 is a comparison of the amino acid sequences of MKK3 (SEQ ID NO:2), MKK4- α (SEQ ID NO:6), the human MAP kinase kinases MEK1 (SEQ ID NO:11) and MEK2 (SEQ ID
10 NO:12), and the yeast HOG1 MAP kinase kinase PBS2 (SEQ ID NO:13). Sequences were compared using the PILE-UP program (version 7.2; Wisconsin Genetics Computer Group). The protein sequences are presented in single letter code (A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His;
15 I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp, and Y, Tyr). The PBS2 sequence is truncated at both the NH₂- (<) and COOH- (>) termini. Gaps introduced into the sequences to optimize the alignment are illustrated by a dash.
20 Identical residues are indicated by a period. The sites of activating phosphorylation in MEK are indicated by asterisks.

Fig. 2A is a dendrogram showing the relationship between members of the human and yeast MAP kinase
25 kinases. The dendrogram was created by the unweighted pair-group method with the use of arithmetic averages (PILE-UP program). The human (hu) MAP kinase kinases MEK1, MEK2, MKK3, and MKK4; the *Saccharomyces cerevisiae* (sc) MAP kinase kinases PBS2, MKK1, and STE7; and the
30 *Saccharomyces pombe* (sp) MAP kinase kinases WIS1 and BYR1 are presented.

Fig. 2B is a dendrogram showing the relationship between MKKs. The dendrogram was created as described for Fig. 2A.

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Fig. 3 is a schematic representation of the ERK, p38, and JNK signal transduction pathways. MEK1 and MEK2 are activators of the ERK subgroup of MAP kinase. MKK3 and MKK4 are activators of the p38 MAP kinase. MKK4 is identified as an activator of both the p38 and JNK subgroups of MAP kinase.

Figs. 4A-4D are a representation of the nucleic acid (SEQ ID NO:1) and amino acid sequences (SEQ ID NO:2) for MKK3.

10 Figs. 5A-5C are a representation of the nucleic acid (SEQ ID NO:3) and amino acid sequences (SEQ ID NO:4) for MKK6.

Figs. 6A-6F are a representation of the nucleic acid (SEQ ID NO:5) and amino acid sequences (SEQ ID NO:6) for MKK4 α .

15 Figs. 7A-7F are a representation of the nucleic acid (SEQ ID NO:7) and amino acid sequences (SEQ ID NO:8) for MKK4 β .

Figs. 8A-8F are a representation of the nucleic acid (SEQ ID NO:9) and amino acid sequences (SEQ ID NO:10) for MKK4 γ .

Fig. 9 is a representation of the deduced primary structure of MKK7 (SEQ ID NO:18) compared with hep (SEQ ID NO:21), the MAP kinase kinases MEK1 (MKK1; SEQ ID NO:11), MEK2 (MKK2; SEQ ID NO:12), MKK3 (SEQ ID NO:2), MKK4 γ (SEQ ID NO:10), MKK5 (SEQ ID NO:22), and MKK6 (SEQ ID NO:4) using the PILE-UP program (version 7,2; Wisconsin Genetics Computer Group). Gaps introduced into the sequences to optimize the alignment are illustrated with a dash (-). Identity is indicated with a dot (.). The sites of activating phosphorylation of MAP kinase kinases (2, 27, 37, and 38) are indicated with asterisks (*).

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Figs. 10A-10D are a representation of the nucleic acid (SEQ ID NO:17) and amino acid (SEQ ID NO:18) sequences for MKK7.

5 Figs. 11A-11D are a representation of the nucleic acid (SEQ ID NO:19) and amino acid (SEQ ID NO:20) sequences of MKK7b.

Figs. 12A-12B are a representation of the nucleic acid (SEQ ID NO:25) and amino acid (SEQ ID NO:26) sequences of human MKK7.

10 Figs. 13A-13D are a representation of the nucleic acid (SEQ ID NO:27) and amino acid (SEQ ID NO:28) sequences of murine MKK7c.

Figs. 14A-14D are a representation of the nucleic acid (SEQ ID NO:29) and amino acid (SEQ ID NO:30) sequences of murine MKK7d.

15 Figs. 15A-15D are a representation of the nucleic acid (SEQ ID NO:31) and amino acid (SEQ ID NO:32) sequences of murine MKK7e.

Fig. 16A is a graph of data from a transfection assay in which cells were co-transfected with AP-1 reporter plasmid pTRE-Luciferase with expression vectors for MKK4, MKK7, JNK1, JNK1(APF), or control vector.

Fig. 16B is a graph of a transfection assay in which cells were co-transfected with a GAL4-ATF2 fusion vector and an expression vector for MKK4, MKK7, JNK1, JNK1(APF), or control vector.

Human Mitogen-Activated Protein Kinase Kinases

The human MAP kinase kinases MKK3 and MKK4 (MKK3/4), and MKK7, described herein mediate the transduction of specific signals from the cell surface to the nucleus along specific pathways. These signal transduction pathways are initiated by factors such as cytokines, UV radiation, osmotic shock, and oxidative stress. Activation of MKK3/4, MKK6, and MKK7 results in

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activation of the MAP kinases. p38 is activated by MKK3 and MKK4. JNK is activated by MKK4 and MKK7. p38 and JNK in turn activate a group of related transcription factors such as ATF2, ATF α , and CRE-BPa. These transcription
5 factors in turn activate expression of specific genes. For example, ATF2 is known to activate expression of human T cell leukemia virus 1 (Wagner and Green (1993) Science 262:395), transforming growth factor-b2 (Kim et al. (1992) *supra*), interferon- β (Du et al. (1993) Cell
10 74:887), and E-selectin (DeLuca et al. (1994) J. Biol. Chem. 269:19193). In addition, ATF2 is implicated in the function of a T cell-specific enhancer (Georgopoulos et al. (1992) Mol. Cell. Biol. 12:747).

The JNK group of MAP kinases is activated by
15 exposure of cells to environmental stress or by treatment of cells with pro-inflammatory cytokines (Gupta et al. (1994) EMBO J. 15:2760-2770; Dérijard et al. (1991) Cell 76:1025-1037; Kyriakis et al. (1994) Nature 369:156-160; Sluss et al. (1994) Mol. Cell. Biol. 14:8376-8384;
20 Kallunki et al. (1994) Genes & Dev. 8:2996-3007). Targets of the JNK signal transduction pathway include the transcription factors ATF2 and c-jun (Whitmarsh & Davis (1996) J. Mol. Med. 74:589-607). These transcription factors are members of the bZIP group that
25 bind as homo- and hetero-dimeric complexes to AP-1 and AP-1-like sites in the promoters of many genes (Curran & Franza (1988) Cell 55:395-397). JNK binds to an NH₂-terminal region of ATF2 and c-Jun and phosphorylates two sites within the activation domain of each transcription
30 factor (Dérijard et al. (1994) Cell 76:1025-1037; van Dam et al. (1995) EMBO J. 14:1798-1811; Livingstone et al. (1995) EMBO J. 14:1785-1797). This phosphorylation leads to increased transcriptional activity (Whitmarsh, *supra*). Together, these biochemical studies indicate that the JNK
35 signal transduction pathway contributes to the regulation

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of AP-1 transcriptional activity in response to cytokines and environmental stress (Whitmarsh, *supra*). Strong support for this hypothesis is provided by genetic evidence indicating that the JNK signaling pathway is
5 required for the normal regulation of AP-1 transcriptional activity (Yang et al. (1997) Proc. Natl. Acad. Sci. USA, 94:3004-3009).

JNK is activated by dual phosphorylation on Thr-183 and Tyr-185 (Dérjard, *supra*). MKK4 (also known as
10 SEKI) was the first MAP kinase kinase identified as a component of the JNK signal transduction pathway (Dérjard et al. 1995) Science 267:682-685; Lin et al. (1995) Science 268:286-290; Sanchez et al. (1994) Nature 372:794-798). Biochemical studies demonstrate that MKK4
15 phosphorylates and activates JNK (Dérjard et al. (1995) Science 267:682-685; Lin et al. (1995) Science 268:286-290; Sanchez et al. (1994) Nature 372:794-798). However, the function of MKK4 may not be restricted to the JNK signal transduction pathway because MKK4 also
20 phosphorylates and activates p38 MAP kinase (Dérjard et al. (1995) Science 267:682-685; Lin et al. (1995) Science 268:286-290). This specificity of MKK4 to activate both JNK and p38 MAP kinase provides a mechanism that may account for the co-ordinate activation of these MAP
25 kinases in cells treated with cytokines or environmental stress (Davis (1994) Trends Biochem. Sci. 19:470-473). However, this co-ordinate activation is not always observed. For example, JNK activation in the liver correlates with decreased p38 MAP kinase activity
30 (Mendelson et al. (1996) Proc. Natl. Acad. Sci. USA 93:12908-12913). These data suggest that the properties of MKK4 are insufficient to account for the regulation of JNK in vivo.

The isolation of human MKKs is described in
35 Example 1, Example 22, Dérjard et al. ((1995) Science

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267:682-685, hereby specifically incorporated by reference), and Raingeaud et al. ((1995) Mol. Cell. Biol. 16:1247-1255). Distinctive regions of the yeast PBS2 sequence were used to design polymerase chain reaction (PCR) primers. Amplification of human brain mRNA with these primers resulted in the formation of specific products which were cloned into a plasmid vector and sequenced. Two different complementary DNAs (cDNAs) that encoded human protein kinases were identified: one encoding a 36 kD protein (MKK3), and one encoding a 44 kD protein (MKK4). MKK4 includes 3 isoforms that vary slightly at the NH₂-terminal, identified as α , β , and γ . The amino acid sequences of MKK3 (SEQ ID NO:2), MKK4- α (SEQ ID NO:6), MKK4- β (SEQ ID NO:8), and MKK4- γ (SEQ ID NO:10) are shown in Fig. 1. The nucleic acid and amino acid sequences of MKK3 (Fig. 4), MKK6 (Fig. 5), MKK4- α (Fig. 6), MKK4- β (Fig. 7), and MKK4- γ (Fig. 8) are also provided. MKK6 was isolated from a human skeletal muscle library by cross-hybridization with MKK3. Except for differences at the N-terminus, MKK6 is highly homologous to MKK3. Other human MKK3 and MKK4 isoforms that exist can be identified by the method described in Example 1.

The expression of these human MKK isoforms was examined by Northern (RNA) blot analysis of mRNA isolated from eight adult human tissues (Example 2). Both protein kinases were found to be widely expressed in human tissues, with the highest expression seen in skeletal muscle tissue.

The substrate specificity of MKK3 was investigated in an *in vitro* phosphorylation assay with recombinant epitope-tagged MAP kinases (JNK1, p38, and ERK2) as substrates (Example 3). MKK3 phosphorylated p38, but did not phosphorylate JNK1 or ERK2. Phosphoaminoacid analysis of p38 demonstrated the presence of a phosphothreonine and phosphotyrosine. Mutational

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analysis of p38 demonstrated that replacement of phosphorylation sites Thr¹⁸⁰ and Tyr¹⁸² with Ala and Phe, respectively, blocked p38 phosphorylation. These results establish that MKK3 functions *in vitro* as a p38 MAP
5 kinase kinase.

Studies of the *in vitro* substrate specificity of MKK4 are described in Example 4. MKK4 incubated with [γ -³²P]ATP, and JNK1, p38, or ERK2 was found to phosphorylate both p38 and JNK1. MKK4 activation of JNK and p38 was
10 also studied by incubating MKK4 with wild-type or mutated JNK1 or p38. The p38 substrate ATF2 was included in each assay. MKK4 was found to exhibit less autophosphorylation than MKK3. MKK4 was also found to be a substrate for activated MAP kinase. Unlike MKK3, MKK4
15 was also found to activate JNK1. MKK4 incubated with wild-type JNK1, but not mutated JNK1, resulted in increased phosphorylation of ATF2. These results establish that MKK4 is a p38 MAP kinase kinase that also phosphorylates the JNK subgroup of MAP kinases.

20 *In vivo* activation of p38 by UV-stimulated MKK3 is described in Example 5. Cells expressing MKK3 were exposed in the presence or absence of UV radiation. MKK3 was isolated by immunoprecipitation and used for protein kinase assays with the substrates p38 or JNK. ATF2 was
25 included in some assays as a substrate for p38 and JNK. MKK3 from non-activated cultured COS cells caused a small amount of phosphorylation of p38 MAP kinase, resulting from basal activity of MKK3. MKK3 from UV-irradiated cells caused increased phosphorylation of p38 MAP kinase,
30 but not of JNK1. An increase in p38 activity was also detected in assays in which ATF2 was included as a substrate. These results establish that MKK3 is activated by UV radiation.

The effect of expression of MKK3 and MKK4 on p38
35 activity was examined in COS-1 cells (Example 6). Cells

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were transfected with a vector encoding p38 and a MEK1, MKK3, or MKK4. Some of the cells were also exposed to EGF or UV radiation. p38 was isolated by immunoprecipitation and assayed for activity with [γ -³²P]ATP and ATF2. The expression of the ERK activator MEK1 did not alter p38 phosphorylation of ATF2. In contrast, expression of MKK3 or MKK4 caused increased activity of p38 MAP kinase. The activation of p38 caused by MKK3 and MKK4 was similar to that observed in UV-irradiated cells, and was much greater than that detected in EGF-treated cells. These *in vitro* results provide evidence that MKK3 and MKK4 activate p38 *in vivo*.

A series of experiments was conducted to examine the potential regulation of ATF2 by JNK1. These experiments are described in Gupta et al. (1995) *Science* 267:389-393, hereby specifically incorporated by reference. The effect of UV radiation on ATF2 phosphorylation was investigated in COS-1 cells transfected with and without epitope-tagged JNK1 (Example 7). Cells were exposed to UV radiation, and JNK1 and JNK2 visualized by in-gel protein kinase assay with the substrate ATF2. JNK1 and JNK2 were detected in transfected and non-transfected cells exposed to UV radiation; however, JNK1 levels were higher in the transfected cells. These results demonstrate that ATF2 is a substrate for the JNK1 and JNK2 protein kinases, and that these protein kinases are activated in cells exposed to UV light.

The site of JNK1 phosphorylation of ATF2 was examined by deletion analysis (Example 8). Progressive NH₂-terminal domain deletion GST-ATF2 fusion proteins were generated, and phosphorylation by JNK1 isolated from UV-irradiated cells was examined. The results showed that JNK1 requires the presence of ATF2 residues 1-60 for phosphorylation of the NH₂-terminal domain of ATF2.

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The ATF2 residues required for binding of JNK1 were similarly examined. JNK1 was incubated with immobilized ATF2, unbound JNK1 was removed by extensive washing, and bound JNK1 was detected by incubation with 5 $[\gamma\text{-}^{32}\text{P}]\text{ATP}$. Results indicate that residues 20 to 60 of ATF2 are required for binding and phosphorylation by JNK1. A similar binding interaction between ATF2 and the 55 kD JNK2 protein kinase has also been observed.

Phosphorylation by JNK1 was shown to reduce the 10 electrophoretic mobility of ATF2 (Example 9). Phosphoamino acid analysis of the full-length ATF2 molecule (residues 1-505) demonstrated that JNK phosphorylated both Thr and Ser residues. The major sites of Thr and Ser phosphorylation were located in the 15 NH_2 and COOH terminal domains, respectively. The NH_2 -terminal sites of phosphorylation were identified as Thr⁶⁹ and Thr⁷¹ by phosphopeptide mapping and mutational analysis. These sites of Thr phosphorylation are located in a region of ATF2 that is distinct from the sub-domain 20 required for JNK binding (residues 20 to 60).

The reduced electrophoretic mobility seen with phosphorylation of ATF2 was investigated further (Example 10). JNK1 was activated in CHO cells expressing JNK1 by treatment with UV radiation, pro-inflammatory cytokine 25 interleukin-1 (IL-1), or serum. A decreased electrophoretic mobility of JNK1-activated ATF2 was observed in cells treated with UV radiation and IL-1. Smaller effects were seen after treatment of cells with serum. These results indicate that ATF2 is an *in vivo* 30 substrate for JNK1.

The effect of UV radiation on the properties of wild-type (Thr^{69,71}) and phosphorylation-defective (Ala^{69,71}) ATF2 molecules was investigated (Example 11). Exposure to UV caused a decrease in the electrophoretic mobility 35 of both endogenous and over-expressed wild-type ATF2.

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This change in electrophoretic mobility was associated with increased ATF2 phosphorylation. Both the electrophoretic mobility shift and increased phosphorylation were blocked by the replacement of Thr⁶⁹ and Thr⁷¹ with Ala in ATF2. This mutation also blocked the phosphorylation of ATF2 on Thr residues *in vivo*.

Transcriptional activities of fusion proteins consisting of the GAL4 DNA binding domain and wild-type or mutant ATF2 were examined (Example 12). Point mutations at Thr⁶⁹ and/or Thr⁷¹ of ATF2 significantly decreased the transcriptional activity of ATF2 relative to the wild-type molecule, indicating the physiological relevance of phosphorylation at these sites for activity.

The binding of JNK1 to the NH₂-terminal activation domain of ATF2 (described in Example 8) suggested that a catalytically inactive JNK1 molecule could function as a dominant inhibitor of the wild-type JNK1 molecule. This hypothesis was investigated by examining the effect of a catalytically inactive JNK1 molecule on ATF2 function (Example 13). A catalytically-inactive JNK1 mutant was constructed by replacing the sites of activating Thr¹⁸³ and Tyr¹⁸⁵ phosphorylation with Ala and Phe, respectively (Ala¹⁸³, Phe¹⁸⁵, termed "dominant-negative"). Expression of wild-type JNK1 caused a small increase in serum-stimulated ATF2 transcriptional activity. In contrast, dominant-negative JNK1 inhibited both control and serum-stimulated ATF2 activity. This inhibitory effect results from the non-productive binding of the JNK1 mutant to the ATF2 activation domain, effectively blocking ATF2 phosphorylation.

The tumor suppressor gene product Rb binds to ATF2 and increases ATF2-stimulated gene expression (Kim et al. (1992) Nature 358:331). Similarly, the adenovirus oncoprotein E1A associates with the DNA binding domain of ATF2 and increases ATF2-stimulated gene expression by a

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mechanism that requires the NH₂-terminal activation domain of ATF2 (Liu and Green (1994) Nature 368:520). ATF2 transcriptional activity was investigated with the luciferase reporter gene system in control, Rb-treated, and E1A-treated cells expressing wild-type or mutant ATF2 molecules (Example 14). Rb and E1A were found to increase ATF2-stimulated gene expression of both wild-type and mutant ATF2. However, mutant ATF2 caused a lower level of reporter gene expression than did wild-type ATF2. Together, these results indicate a requirement for ATF2 phosphorylation (on Thr⁶⁹ and Thr⁷¹) plus either Rb or E1A for maximal transcriptional activity. Thus, Rb and E1A act in concert with ATF2 phosphorylation to control transcriptional activity.

A series of experiments were conducted to examine the action of p38 activation and to establish the relationship of the p38 MAP kinase pathway to the ERK and JNK signal transduction pathways (Raingeaud et al. (1995) J. Biol. Chem. 270:7420, hereby specifically incorporated by reference). Initially, the substrate specificity of p38 was investigated by incubating p38 with proteins that have been demonstrated to be substrates for the ERK and/or JNK groups of MAP kinases (Example 15). We examined the phosphorylation of MBP (Erickson et al. (1990) J. Biol. Chem. 265:19728), EGF-R (Northwood et al. (1991) J. Biol. Chem. 266:15266), cytoplasmic phospholipase A₂ (cPLA₂) (Lin et al. (1993) Cell 72:269), c-Myc (Alvarez et al. (1991) J. Biol. Chem. 266:15277), IκB, c-Jun, and wild-type (Thr^{69,71}) or mutated (Ala^{69,71}) ATF2. p38 phosphorylated MBP and EGF-R, and to a lesser extent IκB, but not the other ERK substrates, demonstrating that the substrate specificity of p38 differs from both the ERK and JNK groups of MAP kinases. Wild-type ATF2, but not mutated ATF2 (Ala^{69,71}), was found to be an excellent p38 substrate.

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The phosphorylation of ATF2 by p38 was associated with an electrophoretic mobility shift of ATF2 during polyacrylamide gel electrophoresis. We tested the hypothesis that p38 phosphorylates ATF2 at the same sites
5 as JNK1 by replacing Thr⁶⁹ and Thr⁷¹ with Ala (Ala^{69,71}). It was found that p38 did not phosphorylate mutated ATF2, which demonstrates that p38 phosphorylates ATF2 within the NH₂-terminal activation domain on Thr⁶⁹ and Thr⁷¹.

A comparison of the binding of JNK and p38 to ATF2
10 was conducted by incubating extracts of cells expressing JNK1 or p38 with epitope alone (GST) or GST-ATF2 (residues 1-109 containing the activation domain) (Example 16). Bound protein kinases were detected by Western blot analysis. The results demonstrate that both
15 p38 and JNK bind to the ATF2 activation domain.

EGF and phorbol ester are potent activators of the ERK signal transduction pathway (Egan and Weinberg (1993) Nature 365:781), causing maximal activation of the ERK sub-group of MAP kinases. These treatments, however,
20 cause only a small increase in JNK protein kinase activity (Dérillard et al. (1994) *supra*; Hibi et al. (1993) *supra*). The effects of EGF or phorbol esters, as well UV radiation, osmotic shock, interleukin-1, tumor necrosis factor, and LPS, on p38 activity were all tested
25 (Example 17). Significantly, EGF and phorbol ester caused only a modest increase in p38 protein kinase activity, whereas environmental stress (UV radiation and osmotic shock) caused a marked increase in the activity of both p38 and JNK. Both p38 and JNK were activated in
30 cells treated with pro-inflammatory cytokines (TNF and IL-1) or endotoxic LPS. Together, these results indicate that p38, like JNK, is activated by a stress-induced signal transduction pathway.

ERKs and JNKs are activated by dual
35 phosphorylation within the motifs Thr-Glu-Tyr and Thr-

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Pro-Tyr, respectively. In contrast, p38 contains the related sequence Thr-Gly-Tyr. To test whether this motif is relevant to the activation of p38, the effect of the replacement of Thr-Gly-Tyr with Ala-Gly-Phe was examined (Example 18). The effect of UV radiation on cells expressing wild-type (Thr¹⁸⁰, Tyr¹⁸²) or mutant p38 (Ala¹⁸⁰, Phe¹⁸²) was studied. Western blot analysis using an anti-phosphotyrosine antibody demonstrated that exposure to UV radiation caused an increase in the Tyr phosphorylation of p38. The increased Tyr phosphorylation was confirmed by phosphoamino acid analysis of p38 isolated from [γ -³²P]phosphate-labeled cells. This analysis also demonstrated that UV radiation caused increased Thr phosphorylation of p38. Significantly, the increased phosphorylation on Thr¹⁸⁰ and Tyr¹⁸² was blocked by the Ala¹⁸⁰/Phe¹⁸² mutation. This result demonstrates that UV radiation causes increased activation of p38 by dual phosphorylation.

It has recently been demonstrated that ERK activity is regulated by the mitogen-induced dual specificity phosphatases MKP1 and PAC1 (Ward et al. (1994) Nature 367:651). The activation of p38 by dual phosphorylation (Example 18) raises the possibility that p38 may also be regulated by dual specificity phosphatases. We examined the effect of MKP1 and PAC1 on p38 MAP kinase activation (Example 19). Cells expressing human MKP1 and PAC1 were treated with and without UV radiation, and p38 activity measured. The expression of PAC1 or MKP1 was found to inhibit p38 activity. The inhibitory effect of MKP1 was greater than PAC1. In contrast, cells transfected with a catalytically inactive mutant phosphatase (mutant PAC1 Cys²⁵⁷/Ser) did not inhibit p38 MAP kinase. These results demonstrate that p38 can be regulated by dual specificity phosphatases PAC1 and MKP1.

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The sub-cellular distribution of p38 MAP kinase was examined by indirect immunofluorescence microscopy (Example 20). Epitope-tagged p38 MAP kinase was detected using the M2 monoclonal antibody. Specific staining of
5 cells transfected with epitope-tagged p38 MAP kinase was observed at the cell surface, in the cytoplasm, and in the nucleus. Marked changes in cell surface and nuclear p38 MAP kinase were not observed following UV
10 irradiation, but an increase in the localization of cytoplasmic p38 MAP kinase to the perinuclear region was detected.

A series of experiments were conducted to study the activation of JNK by hyper-osmotic media (Example 21). These experiments were reported by Galcheva-Gargova
15 et al. (1994) Science 265:806, hereby specifically incorporated by reference. CHO cells expressing epitope-tagged JNK1 were incubated with 0 - 1000 mM sorbitol, and JNK1 activity measured in an immune complex kinase assay with the substrate c-Jun. Increased JNK1 activity was
20 observed in cells incubated for 1 hour with 100 mM sorbitol. Increased JNK1 activity was observed within 5 minutes of exposure to 300 mM sorbitol. Maximal activity was observed 15 to 30 minutes after osmotic shock with a progressive decline in JNK1 activity at later times. The
25 activation of JNK by osmotic shock was studied in cells expressing wild-type (Thr¹⁸³, Tyr¹⁸⁵) or mutated (Ala¹⁸³, Phe¹⁸⁵) JNK1. JNK1 activity was measured after incubation for 15 minutes with or without 300 mM sorbitol. Cells expressing wild-type JNK1 showed increased JNK1 activity,
30 while cells expressing mutated JNK1 did not. These results demonstrate that the JNK signal transduction pathway is activated in cultured mammalian cells exposed to hyper-osmotic media.

The results of the above-described experiments are
35 illustrated in Fig. 3, which diagrams the ERK, p38, and

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JNK MAP kinase signal transduction pathways. ERKs are
potently activated by treatment of cells with EGF or
phorbol esters. In contrast, p38 is only slightly
activated under these conditions (Example 15). However,
5 UV radiation, osmotic stress, and inflammatory cytokines
cause a marked increase in p38 activity. This difference
in the pattern of activation of ERK and p38 suggests that
these MAP kinases are regulated by different signal
transduction pathways. The molecular basis for the
10 separate identity of these signal transduction pathways
is established by the demonstration that the MAP kinase
kinases that activate ERK (MEK1 and MEK2) and p38 (MKK3,
MKK4, and MKK6) are distinct.

The isolation of murine and human MKK7 is
15 described in Example 22. Distinctive regions of the
Drosophila MAP kinase kinase *hep* sequence were used to
design polymerase chain reaction (PCR) primers.
Amplification of murine testis mRNA with these primers
resulted in the formation of specific products which were
20 cloned into a plasmid vector and sequenced. One sequence
related to *hep* was identified and used to screen a murine
testis library. Five DNAs (cDNAs) that encoded protein
kinases were identified: one encoding a MAP protein
kinase kinase (MKK7). The others encoded various splice
25 variants: MKK7b (a partial sequence appears in Fig. 11),
MKK7c (Fig. 13), MKK7d (Fig. 14), MKK7e (Fig. 15). The
deduced amino acid sequences of MKK7 (SEQ ID NO:18) and
hep (SEQ ID NO:21) are shown in Fig. 9, and compared to
the MAP kinase kinases MEK1 (SEQ ID NO:11), MEK2 (SEQ ID
30 NO:12), MKK3 (SEQ ID NO:2), MKK4 (SEQ ID NO:10), MKK5
(SEQ ID NO:22), and MKK6 (SEQ ID NO:4). A human MKK7 was
identified by screening a human cDNA library with a full-
length (mouse) MKK7 cDNA probe. The identified partial
sequence (lacking the 3' end) is homologous to mouse
35 MKK7c.

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The expression of MKK7 and MKK4 isoforms was examined by Northern (RNA) blot analysis of poly A+ mRNA isolated from eight murine tissues (Example 23). Both protein kinases were found to be widely expressed.

5 The substrate specificity of MKK7 was investigated in an *in vitro* phosphorylation assay with recombinant, epitope-tagged MAP kinases (JNK1, p38, and ERK2) as substrates (Example 24). MKK7 phosphorylated JNK, but did not phosphorylate p38 or ERK2. MKK7 was
10 phosphorylated by p38 and JNK1.

MKK7 was found to specifically activate JNK protein kinase *in vivo* (Example 25). CHO cells were co-transfected with an epitope-tagged MAP kinase (JNK1, p38, or ERK2) together with an empty expression vector or an
15 expression vector encoding MKK1, MKK4, MKK6, or MKK7 and the product of the phosphorylation reaction analyzed. MKK7 activated only JNK1, and did so to a greater extent than did MKK4.

To test whether MKK7 could cause increased AP-1
20 transcriptional activity, a co-transfection assay was employed (Example 26). Co-expression of MKK7 with JNK caused an increase in AP-1 reporter gene expression that was greater than the increase seen with MKK4 and JNK. A similar result was seen when ATF2 was used as the
25 reporter gene. In addition, MKK7 alone was able to increase expression of ATF2 (Fig. 16).

MKK isoforms are useful for screening reagents which modulate MKK activity. Described in the Use
section following the Examples are methods for
30 identifying reagents capable of inhibiting or activating MKK activity.

The discovery of human MKK isoforms and MKK-mediated signal transduction pathways is clinically significant for the treatment of MKK-mediated disorders.
35 One use of the MKK isoforms is in a method for screening

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reagents able to inhibit or prevent the activation of the MKK-MAP kinase- ATF2 pathways.

EXAMPLES

The following examples are meant to illustrate,
5 not limit, the invention.

Example 1. MKK Protein Kinases

The primary sequences of MKK3 and MKK4 were deduced from the sequence of cDNA clones isolated from a human fetal brain library.

10 The primers TTYTAYGGNGCNTTYTTYATHGA (SEQ ID NO:14) and ATBCTYTCNGGNGCCATKTA (SEQ ID NO:15) were designed based on the sequence of PBS2 (Brewster et al. (1993) Science 259:1760; Maeda et al. (1994) Nature 369:242). The primers were used in a PCR reaction with human brain
15 mRNA as template. Two sequences that encoded fragments of PBS2-related protein kinases were identified. Full-length human cDNA clones were isolated by screening of a human fetal brain library (Dérillard et al. (1995) Science 267:682-685). The cDNA clones were examined by
20 sequencing with an Applied Biosystems model 373A machine. The largest clones obtained for MKK3 (2030 base pairs (bp)) and MKK4 (3576 bp) contained the entire coding region of these protein kinases.

The primary structures of MKK3 (SEQ ID NO:2) and
25 MKK4- α (SEQ ID NO:6) are shown in Fig. 1. An in-frame termination codon is located in the 5' untranslated region of the MKK3 cDNA, but not in the 5' region of the MKK4 cDNA. The MKK4 protein sequence presented starts at the second in-frame initiation codon.

30 These sequences were compared to those of the human MAP kinase kinases MEK1 (SEQ ID NO:11) and MEK2 (SEQ ID NO:12) (Zheng and Guan (1993) J. Biol. Chem 268:11435) and of the yeast MAP kinase kinase PBS2 (SEQ ID NO:13) (Boguslawski and Polazzi (1987) Proc. Natl.

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Acad. Sci. USA 84:5848) (Fig. 1). The identity and similarity of the kinases with human MKK3 (between subdomains I and XI) were calculated with the BESTFIT program (version 7.2; Wisconsin Genetics Computer Group) (percent of identity to percent of similarity): MEK1, 41%/63%; MEK2, 41%/62%; MKK4 α , 52%/73%; and PBS2, 40%/59%). The identity and similarity of the kinases with human MKK4 α were calculated to be as follows (percent of identity to percent of similarity): MEK1, 44%/63%; MEK2, 45%/61%; MKK3, 52%/73%; and PBS2, 44%/58%.

The cDNA sequences of MKK3 and MKK4 γ have been deposited in GenBank with accession numbers L36719 and L36870, respectively. The MKK4 γ cDNA sequence contains both the cDNA sequences of MKK4 α and MKK4 β , which are generated *in vivo* from alternate splicing sites. One of ordinary skill in the art can readily determine the amino acid sequences of MKK3 and MKK4 isoforms from the deposited cDNA sequences.

Example 2. Expression of MKK3 and MKK4 mRNA in Adult Human Tissue

Northern blot analysis was performed with polyadenylated [poly(A)⁺] mRNA (2 μ g) isolated from human heart, brain, placenta, lung, liver, muscle, kidney, and pancreas tissues. The mRNA was fractionated by denaturing agarose gel electrophoresis and was transferred to a nylon membrane. The blot was probed with the MKK3 and MKK4 cDNA labeled by random priming with [α -³²P]ATP (deoxyadenosine triphosphate) (Amersham International PLC). MKK3 and MKK4 were expressed in all tissues examined; the highest expression of MKK3 and MKK4 was found in skeletal muscle tissue.

The relation between members of the human and yeast MAP kinase kinase group is presented as a

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dendrogram (Fig. 2). MKK3/4 form a unique subgroup of human MAP kinase kinases.

Example 3. In Vitro Phosphorylation of p38 MAP kinase by MKK3

5 GST-JNK1, and GST-ERK2 have been described (Dérijard et al. (1994) *supra*; Gupta et al. (1995) Science 267:389; Wartmann and Davis (1994) J. Biol. Chem. 269:6695, each herein specifically incorporated by reference). GST-p38 MAP kinase was prepared from the
10 expression vector pGStag (Dressier et al. (1992) Biotechniques 13:866) and a PCR fragment containing the coding region of the p38 MAP kinase cDNA. GST-MKK3 and MKK4 were prepared with pGEX3X (Pharmacia-LKB Biotechnology) and PCR fragments containing the coding
15 region of the MKK3 and MKK4 cDNAs. The GST fusion proteins were purified by affinity chromatography with the use of GSH-agarose (Smith and Johnson (1988) Gene 67:31). The expression vectors pCMV-Flag-JNK1 and pCMV-MEK1 have been described (Dérijard et al. (1994) *supra*;
20 Wartmann and Davis (1994) *supra*). The plasmid pCMV-Flag-p38 MAP kinase was prepared with the expression vector pCMV5 (Andersson et al. (1989) J. Biol. Chem. 264:8222) and the p38 MAP kinase cDNA. The expression vectors for MKK3 and MKK4 were prepared by subcloning of the cDNAs
25 into the polylinker of pCDNA3 (Invitrogen). The Flag epitope (Asp-Tyr-Lys-Asp-Asp-Asp-Lys (SEQ ID NO:16); Immunex, Seattle, WA) was inserted between codons 1 and 2 of the kinases by insertional overlapping PCR (Ho et al. (1989) Gene 77:51).

30 Protein kinase assays were performed in kinase buffer (25 mM 4-(2-hydroxyethyl)-1-piperazineethansulfonic acid, pH 7.4, 25 mM β -glycerophosphate, 25 mM $MgCl_2$, 2 mM dithiothreitol, and 0.1 mM orthovanadate). Recombinant GST-MKK3 was

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incubated with [γ - 32 P]ATP and buffer, GST-JNK1, GST-p38 MAP kinase, or GST-ERK2. The assays were initiated by the addition of 1 μ g of substrate proteins and 50 μ M [γ - 32 P]ATP (10 Ci/mmol) in a final volume of 25 μ l. The reactions were terminated after 30 minutes at 25°C by addition of Laemmli sample buffer. The phosphorylation of the substrate proteins was examined after SDS-polyacrylamide gel electrophoresis (SDS-PAGE) by autoradiography. Phosphoaminoacid analysis was performed by partial acid hydrolysis and thin-layer chromatography (Dérillard et al. (1994) *supra*; Alvarez et al. (1991) J. Biol. Chem. 266:15277). Autophosphorylation of MKK3 was observed in all groups. MKK3 phosphorylated p38 MAP kinase, but not JNK1 or ERK2.

A similar insertional overlapping PCR procedure was used to replace Thr¹⁸⁰ and Tyr¹⁸² of p38, with Ala and Phe, respectively. The sequence of all plasmids was confirmed by automated sequencing on an Applied Biosystems model 373A machine. GST-MKK3 was incubated with [γ - 32 P]ATP and buffer, wild-type GST-p38 MAP kinase (TGY), or mutated GST-p38 MAP kinase (AGF). The phosphorylated proteins were resolved by SDS-PAGE and detected by autoradiography. Only phosphorylation of wild-type p38 was observed.

Example 4. In Vitro Phosphorylation and Activation of JNK and p38 MAP Kinase by MKK4

Protein kinase assays were conducted as described in Example 3. Recombinant GST-MKK4 was incubated with [γ - 32 P]ATP and buffer, GST-JNK1, GST-p38 MAP kinase, or GST-ERK2. JNK1 and p38 were phosphorylated, as was MKK4 incubated with JNK1 and p38.

GST-MKK4 was incubated with [γ - 32 P]ATP and buffer, wild-type JNK1 (Thr¹⁸³, Tyr¹⁸⁵), or mutated GST-JNK1 (Ala¹⁸³, Phe¹⁸⁵). The JNK1 substrate ATF2 (Gupta et al. (1995)

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supra) was included in each incubation. ATF2 was phosphorylated in the presence of MKK4 and wild-type JNK1. The results establish that MKK4 phosphorylates and activates both p38 and JNK1.

5 Example 5. Phosphorylation and Activation of p38 MAP
Kinase by UV-stimulated MKK3

Epitope-tagged MKK3 was expressed in COS-1 cells maintained in Dulbecco's modified Eagle's medium supplemented with fetal bovine serum (5%) (Gibco-BRL).

10 The cells were transfected with the lipofectamine reagent according to the manufacturer's recommendations (Gibco-BRL) and treated with UV radiation or EGF as described (Dérillard et al. (1994) *supra*).

The cells were exposed in the absence and presence
15 of UV-C (40 J/m²). The cells were solubilized with lysis buffer (20 mM tris, pH 7.4, 1% TRITON® X-100, 10% glycerol, 137 mM NaCl, 2 mM EDTA, 25 mM β -glycerophosphate, 1 mM Na orthovanadate, 1 mM phenylmethylsulfonyl fluoride, and leupeptin (10 μ g/ml))
20 and centrifuged at 100,000 x g for 15 minutes at 4°C. MKK3 was isolated by immunoprecipitation. The epitope-tagged protein kinases were incubated for 1 hour at 4°C with the M2 antibody to the Flag epitope (IBI-Kodak) bound to protein G-Sepharose (Pharmacia-LKB
25 Biotechnology). The immunoprecipitates were washed twice with lysis buffer and twice with kinase buffer.

Protein kinase assays were conducted with the substrate GST-p38 MAP kinase or JNK1. ATF2 was included in some assays. Basal levels of MKK3 phosphorylation of
30 p38 MAP kinase were observed. UV-irradiation resulted in increased phosphorylation of p38 MAP kinase, but not of JNK1. The increased p38 MAP kinase activity resulted in increased phosphorylation of ATF2.

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Example 6. Activation of p38 MAP Kinase in Cells
Expressing MKK3 and MKK4

COS-1 cells were transfected with epitope-tagged p38 MAP kinase, together with an empty expression vector
5 or an expression vector encoding MEK1, MKK3, or MKK4 α . Some of the cultures were exposed to UV radiation (40 J/m²) or treated with 10 nM EGF. p38 MAP kinase was isolated by immunoprecipitation with M2 monoclonal antibody, and the protein kinase activity was measured in
10 the immunocomplex with [γ -³²P]ATP and ATF2 as substrates. The product of the phosphorylation reaction was visualized after SDS-PAGE by autoradiography. ATF2 was not phosphorylated in the control MEK1, or EGF-treated groups, but was phosphorylated in the MKK3, MKK4, and UV-
15 irradiated groups. MKK3 and MKK4 phosphorylation of ATF2 was similar to that seen with p38 MAP kinase isolated from UV-irradiated cells.

Example 7. Phosphorylation of ATF2 by JNK1 and JNK2

COS-1 cells were maintained in Dulbecco's modified
20 Eagle's medium supplemented with bovine serum albumin (5%) (Gibco-BRL). Metabolic labeling with [³²]P was performed by incubation of cells for 3 hours in phosphate-free modified Eagle's medium (Flow Laboratories Inc.) supplemented with [³²P]orthophosphate (2 mCi/ml)
25 (Dupont-NEN). COS-1 cells were transfected without (Mock) and with epitope-tagged JNK1 (JNK1). Plasmid expression vectors encoding the JNK1 cDNA have previously been described (Dérillard et al. (1994) Cell 76:1025, herein specifically incorporated by reference). Plasmid
30 DNA was transfected into COS-1 cells by the lipofectamine method (Gibco-BRL). After 48 hours of incubation, some cultures were exposed to 40 J/m² UV radiation and incubated for 1 hour at 37°C.

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Cells were lysed in 20 mM Tris, pH 7.5, 25 mM β -glycerophosphate, 10% glycerol, 1% Triton® X-100, 0.5% (w/v) deoxycholate, 0.1% (w/v) SDS, 0.137 M NaCl, 2 mM pyrophosphate, 1 mM orthovanadate, 2 mM EDTA, 10 μ g/ml leupeptin, 1 mM PMSF. Soluble extracts were prepared by centrifugation in a microfuge for 20 minutes at 4°C. JNK1 immunoprecipitates were also prepared by reaction with a rabbit antiserum prepared with recombinant JNK1 as an antigen.

10 In-gel protein kinase assays were performed with cell lysates and JNK1 immunoprecipitates after SDS-PAGE by renaturation of protein kinases, polymerization of the substrate (GST-ATF2, residues 1-505) in the gel, and incubation with [γ - 32 P]ATP (Dérillard et al. (1994) *supra*).
15 The incorporation of [32 P]phosphate was visualized by autoradiography and quantitated with a Phosphorimager and ImageQuant software (Molecular Dynamics Inc., Sunnyvale, CA). The cell lysates demonstrate the presence of 46 kD and 55 kD protein kinases that phosphorylate ATF2 in
20 extracts prepared from UV-irradiated cells. The 46 kD and 55 kD protein kinases were identified as JNK1 and JNK2, respectively.

Example 8. Binding of JNK1 to ATF2 and Phosphorylation of the NH₂-Terminal Activation Domain

25 The site of JNK1 phosphorylation of ATF2 was investigated by generation of progressive NH₂-terminal domain deletions of ATF2. Plasmid expression vectors encoding ATF2 (pECE-ATF2) (Liu and Green (1994) and (1990)), have been described. Bacterial expression
30 vectors for GST-ATF2 fusion proteins were constructed by sub-cloning ATF2 cDNA fragments from a polymerase chain reaction (PCR) into pGEX-3X (Pharmacia-LKB Biotechnology Inc.). The sequence of all constructed plasmids was confirmed by automated sequencing with an Applied

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Biosystems model 373A machine. The GST-ATF2 proteins were purified as described (Smith and Johnson (1988) Gene 67:31), resolved by SDS-PAGE and stained with Coomassie blue. GST-ATF2 fusion proteins contained residues 1-505, 1-349, 350-505, 1-109, 20-109, 40-109, and 60-109.

The phosphorylation of GST-ATF2 fusion proteins by JNK1 isolated from UV-irradiated cells was examined in an immunocomplex kinase assay. Immunocomplex kinase assays were performed with Flag epitope-tagged JNK1 and the monoclonal antibody M2 (IBI-Kodak) as described by Dérijard et al. (1994) *supra*). Immunocomplex protein kinase assays were also performed with a rabbit antiserum prepared with recombinant JNK1 as an antigen. The cells were solubilized with 20 mM Tris, pH 7.5, 10% glycerol, 1% Triton® X-100, 0.137 M NaCl, 25 mM β -glycerophosphate, 2 mM EDTA, 1 mM orthovanadate, 2 mM pyrophosphate, 10 μ g/ml leupeptin, and 1 mM PMSF. JNK1 was immunoprecipitated with protein G-Sepharose bound to a rabbit polyclonal antibody to JNK or the M2 monoclonal antibody to the Flag epitope. The beads were washed three times with lysis buffer and once with kinase buffer (20 mM Hepes, pH 7.6, 20 mM $MgCl_2$, 25 mM β -glycerophosphate, 100 μ M Na orthovanadate, 2 mM dithiothreitol). The kinase assays were performed at 25°C for 10 minutes with 1 μ g of substrate, 20 μ M adenosine triphosphate and 10 μ Ci of [γ - 32 P]ATP in 30 μ l of kinase buffer. The reactions were terminated with Laemmli sample buffer and the products were resolved by SDS-PAGE (10% gel). JNK1 phosphorylates GST-ATF2 fusion proteins containing residues 1-505, 1-349, 1-109, 20-109, and 40-109, but not 60-109. These results indicate that the presence of ATF2 residues 1-60 are required for phosphorylation by JNK.

The binding of immobilized GST-ATF2 fusion proteins was examined in a solid-phase kinase assay as

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described by Hibi et al. ((1993) Genes Dev. 7:2135, herein specifically incorporated by reference). JNK1 from UV-irradiated cells was incubated with GST-ATF2 fusion proteins bound to GSH-agarose. The agarose beads
5 were washed extensively to remove the unbound JNK1. Phosphorylation of the GST-ATF2 fusion proteins by the bound JNK1 protein kinase was examined by addition of [γ - 32 P]ATP. JNK1 bound GST-ATF2 fusion proteins containing residues 1-505, 1-349, 1-109, 20-109, and 40-109,
10 indicating that the presence of residues 20-60 were required for binding of JNK1 to ATF2.

Example 9. Phosphorylation of the NH₂-terminal
Activation Domain of ATF2 on Thr⁶⁹ and Thr⁷¹
by JNK1

15 The effect of UV radiation on the properties of wild-type (Thr^{69,71}) and phosphorylation-defective (Ala^{69,71}) ATF2 molecules was examined. Mock-transfected and JNK1-transfected COS cells were treated without and with 40 J/m² UV radiation. The epitope-tagged JNK1 was isolated
20 by immunoprecipitation with the M2 monoclonal antibody. The phosphorylation of GST-ATF2 (residues 1 to 109) was examined in an immunocomplex kinase assay as described above. The GST-ATF2 was resolved from other proteins by SDS-PAGE and stained with Coomassie blue. The
25 phosphorylation of GST-ATF2 was detected by autoradiography. JNK1-transfected cells, but not mock-transfected cells, phosphorylated ATF2. JNK1 phosphorylation of ATF2 was greater in cells exposed to UV radiation. Phosphorylation of ATF2 by JNK1 was
30 associated with a decreased electrophoretic mobility.

In a separate experiment, GST fusion proteins containing full-length ATF2 (residues 1 to 505), an NH₂-terminal fragment (residues 1 to 109), and a COOH-terminal fragment (residues 95 to 505) were

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phosphorylated with JNK1 and the sites of phosphorylation analyzed by phosphoamino acid analysis. The methods used for phosphopeptide mapping and phosphoamino acid analysis have been described (Alvarez et al. (1991) J. Biol. Chem. 266:15277). The horizontal dimension of the peptide maps was electrophoresis and the vertical dimension was chromatography. The NH₂-terminal sites of phosphorylation were identified as Thr⁶⁹ and Thr⁷¹ by phosphopeptide mapping and mutational analysis. Site-directed mutagenesis was performed as described above, replacing Thr⁶⁹ and Thr⁷¹ with Ala. Phosphorylation of mutated ATF2 was not observed.

Example 10. Reduced Electrophoretic Mobility of JNK-Activated ATF2

CHO cells were maintained in Ham's F12 medium supplemented with 5% bovine serum albumin (Gibco-BRL). Cells were labeled and transfected with JNK1 as described above. CHO cells were treated with UV-C (40 J/m²), IL-1 α (10 ng/ml) (Genzyme), or fetal bovine serum (20%) (Gibco-BRL). The cells were incubated for 30 minutes at 37°C prior to harvesting. The electrophoretic mobility of ATF2 after SDS-PAGE was examined by protein immuno-blot analysis. A shift in ATF2 electrophoretic mobility was observed in cells treated with UV, IL-1, and serum. These results indicate that JNK1 activation is associated with an electrophoretic mobility shift of ATF2, further suggesting that ATF2 is an *in vivo* substrate for JNK1.

Example 11. Increased ATF2 Phosphorylation After Activation of JNK

COS-1 cells were transfected without (control) and with an ATF2 expression vector (ATF2), as described above (Hai et al. (1989) *supra*). The effect of exposure of the cells to 40 J/m² UV-C was examined. After irradiation,

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the cells were incubated for 0 or 30 minutes (control) or 0, 15, 30, and 45 minutes (ATF2) at 37°C and then collected. The electrophoretic mobility of ATF2 during SDS-PAGE was examined by protein immuno-blot analysis as described above. The two electrophoretic mobility forms of ATF2 were observed in ATF2-transfected cells, but not in control cells.

The phosphorylation state of wild-type (Thr^{69,71}) ATF2 and mutated (Ala^{69,71}) ATF2 was examined in cells labeled with [³²]P, treated without and with 40 J/m² UV-C, and then incubated at 37°C for 30 minutes (Hai et al. (1989) *supra*). The ATF2 proteins were isolated by immunoprecipitation and analyzed by SDS-PAGE and autoradiography. The phosphorylated ATF2 proteins were examined by phosphoamino acid analysis as described above. Both forms of ATF2 contained phosphoserine, but only wild-type ATF2 contained phosphothreonine.

Tryptic phosphopeptide mapping was used to compare ATF2 phosphorylated *in vitro* by JNK1 with ATF2 phosphorylated in COS-1 cells. A map was also prepared with a sample composed of equal amounts of *in vivo* and *in vitro* phosphorylated ATF2 (Mix). Mutation of ATF2 at Thr⁶⁹ and Thr⁷¹ resulted in the loss of two tryptic phosphopeptides in maps of ATF2 isolated from UV-irradiated cells. These phosphopeptides correspond to mono- and bis-phosphorylated peptides containing Thr⁶⁹ and Thr⁷¹. Both of these phosphopeptides were found in maps of ATF2 phosphorylated by JNK1 *in vitro*.

Example 12. Inhibition of ATF2-Stimulated Gene Expression by Mutation of the Phosphorylation Sites Thr⁶⁹ and Thr⁷¹

A fusion protein consisting of ATF2 and the GAL4 DNA binding domain was expressed in CHO cells as described above. The activity of the GAL4-ATF2 fusion

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protein was measured in co-transfection assays with the reporter plasmid pG5E1bLuc (Seth et al. (1992) J. Biol. Chem. 267:24796, hereby specifically incorporated by reference). The reporter plasmid contains five GAL4
 5 sites cloned upstream of a minimal promoter element and the firefly luciferase gene. Transfection efficiency was monitored with a control plasmid that expresses β -galactosidase (pCH110; Pharmacia-LKB Biotechnology). The luciferase and β -galactosidase activity detected in cell
 10 extracts was measured as the mean activity ratio of three experiments (Gupta et al. (1993) Proc. Natl. Acad. Sci. USA 90:3216, hereby specifically incorporated by reference). The results, shown in Table 1, demonstrate the importance of phosphorylation at Thr⁶⁹ and Thr⁷¹ for
 15 transcriptional activity.

TABLE 1. INHIBITION OF ATF-2 STIMULATED GENE EXPRESSION BY MUTATION OF THE PHOSPHORYLATION SITES THR^{69,71}

PROTEIN	LUCIFERASE ACTIVITY (Light Units/OD)
GAL4	45
20 GAL4-ATF2 (wild type)	320,000
GAL4-ATF2 (Ala ⁶⁹)	24,000
GAL4-ATF2 (Ala ⁷¹)	22,000
GAL4-ATF2 (Ala ^{69,71})	29,000
GAL4-ATF2 (Glu ⁶⁹)	27,000

25 Example 13. Effect of Dominant-Negative JNK1 Mutant on ATF2 Function

The luciferase reporter plasmid system was used to determine the effect of point mutations at the ATF2 phosphorylation sites Thr⁶⁹ and Thr⁷¹ in serum-treated CHO
 30 cells transfected with wild-type (Thr¹⁸³, Tyr¹⁸⁵) or mutant (Ala¹⁸³, Phe¹⁸⁵) JNK1. Control experiments were done with mock-transfected cells. The CHO cells were serum-starved

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for 18 hours and then incubated without or with serum for 4 hours. Expression of wild-type ATF2 caused a small increase in serum-stimulated ATF2 transcriptional activity. In contrast, mutant JNK1 inhibited both control and serum-stimulated ATF2 activity.

Example 14. Effect of Tumor Suppressor Gene Product Rb and Adenovirus Oncoprotein E1A on ATF2-Stimulated Gene Expression

The effect of expression of the Rb tumor suppressor gene product and adenovirus oncoprotein E1A on ATF2 transcriptional activity were investigated with a luciferase reporter plasmid and GAL4-ATF2 (residues 1-505), as described above. Cells were transfected with wild-type (Thr^{69,71}) or mutated (Ala^{69,71}) ATF2. No effect of Rb or E1A on luciferase activity was detected in the absence of GAL4-ATF2. Rb and E1A were found to increase ATF2-stimulated gene expression of both wild-type and mutated ATF2. However, mutated ATF2 caused a lower level of reporter gene expression than did wild-type ATF2. These results indicate a requirement for ATF2 phosphorylation (on Thr⁶⁹ and Thr⁷¹) plus either Rb or E1A for maximal transcriptional activity.

Example 15. Substrate Specificity of p38 MAP Kinase

Substrate phosphorylation by p38 MAP kinase was examined by incubation of bacterially-expressed p38 MAP kinase with I κ B, cMyc, EGF-R, cytoplasmic phospholipase A₂ (cPLA₂), c-Jun, and mutated ATF2 (Thr^{69,71}) and ATP[γ -³²P] (Raingeaud et al. (1995) J. Biol. Chem 270:7420, herein specifically incorporated by reference). GST-I κ B was provided by Dr D. Baltimore (Massachusetts Institute of Technology). GST-cMyc (Alvarez et al. (1991) J. Biol. Chem. 266:15277), GST-EGF-R (residues 647-688) (Koland et al. (1990) Biochem. Biophys. Res. Commun. 166:90), and GST-c-Jun (Dérijard et al. (1994) *supra*) have been

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described. The phosphorylation reaction was terminated after 30 minutes by addition of Laemmli sample buffer. The phosphorylated proteins were resolved by SDS-PAGE and detected by autoradiography. The rate phosphorylation of the substrate proteins was quantitated by PhosphorImager (Molecular Dynamics Inc.) analysis. The relative phosphorylation of ATF2, MBP, EGF-R, and I κ B was 1.0, 0.23, 0.04, and 0.001, respectively.

Example 16. Binding of p38 MAP Kinase to ATF2

Cell extracts expressing epitope-tagged JNK1 and p38 MAP kinase were incubated with a GST fusion protein containing the activation domain of ATF2 (residues 1-109) immobilized on GSH agarose. The supernatant was removed and the agarose was washed extensively. Western blot analysis of the supernatant and agarose-bound fractions was conducted as follows: proteins were fractionated by SDS-PAGE, electrophoretically transferred to an Immobilon-P membrane, and probed with monoclonal antibodies to phosphotyrosine (PY20) and the Flag epitope (M2). Immunocomplexes were detected using enhanced chemiluminescence (Amersham International PLC). Control experiments were performed using immobilized GST.

Example 17. p38 MAP Kinase and JNK1 Activation by Pro-Inflammatory Cytokines and Environmental Stress

The effect of phorbol ester, EGF, UV radiation, osmotic stress, IL-1, tumor necrosis factor (TNF), and LPS on p38 MAP kinase and JNK1 activity were measured in immunocomplex protein kinase assays using ATP[γ - 32 P] and ATF2 as substrates. TNF α and IL-1 α were from Genzyme Corp. Lipopolysaccharide (LPS) was isolated from lyophilized *Salmonella minnesota* Re595 bacteria as described (Mathison et al. (1988) J. Clin. Invest.

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81:1925). Phorbol myristate acetate was from Sigma. EGF was purified from mouse salivary glands (Davis (1988) J. Biol. Chem. 263:9462). Kinase assays were performed using immunoprecipitates of p38 and JNK. The

5 immunocomplexes were washed twice with kinase buffer (described above), and the assays initiated by the addition of 1 μ g of ATF2 and 50 μ M [γ - 32 P]ATP (10 Ci/mmol) in a final volume of 25 μ l. The reactions were

10 terminated after 30 minutes at 30°C by addition of Laemmli sample buffer. The phosphorylation of ATF2 was examined after SDS-PAGE by autoradiography, and the rate of ATF2 phosphorylation quantitated by PhosphorImager analysis.

The results are shown in Table 2. Exposure of

15 HeLa cells to 10 nM phorbol myristate acetate very weakly activated p38 and JNK1. Similarly, treatment with 10 nM EGF only weakly activated p38 and JNK1. By contrast, treatment with 40 J/m² UV-C, 300 mM sorbitol, 10 ng/ml interleukin-1, and 10 ng/ml TNF α strongly activated p38

20 and JNK1 activity. The effect of LPS on the activity of p38 was examined using CHO cells that express human CD14. Exposure of CHO cells to 10 ng/ml LPS only slightly activated p38 and JNK1 activity.

25 TABLE 2. p38 AND JNK1 ACTIVATION BY PRO-INFLAMMATORY CYTOKINES AND ENVIRONMENTAL STRESS.

Relative Protein Kinase Activity		
	JNK	p38
Control	1.0	1.0
Epidermal Growth Factor (10 nM)	1.9	2.1
30 Phorbol Ester (10 nM)	2.3	2.9
Lipopolysaccharide (10 ng/ml)	3.6	3.7
Osmotic Shock (300 mM sorbitol)	18.1	4.2
Tumor Necrosis Factor (10 ng/ml)	19.3	10.3
Interleukin-1 (10 ng/ml)	8.9	6.2
35 UV (40 J/m ²)	7.4	17.1

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Example 18. p38 MAP Kinase Activation by Dual
Phosphorylation on Tyr and Thr

COS-1 cells expressing wild-type (Thr¹⁸⁰, Tyr¹⁸²) or mutated (Ala¹⁸⁰, Phe¹⁸²) p38 MAP kinase were treated without
5 and with UV-C (40 J/m²). The cells were harvested 30 minutes following exposure with or without UV radiation. Control experiments were performed using mock-transfected cells. The level of expression of epitope-tagged p38 MAP
10 kinase and the state of Tyr phosphorylation of p38 MAP kinase was examined by Western blot analysis using the M2 monoclonal antibody and the phosphotyrosine monoclonal antibody PY20. Immune complexes were detected by enhanced chemiluminescence.

Wild-type and mutant p38 were expressed at similar
15 levels. Western blot analysis showed that UV radiation caused an increase in the Tyr phosphorylation of p38. The increased Tyr phosphorylation was confirmed by phosphoamino acid analysis of p38 isolated from [³²P]phosphate-labeled cells. The results also showed
20 that UV radiation increased Thr phosphorylation of p38. The increased phosphorylation on Tyr and Thr was blocked by mutated p38. Wild-type and mutated p38 were isolated from the COS-1 cells by immunoprecipitation. Protein kinase activity was measured in the immune complex using
25 [γ -³²P]ATP and GST-ATF2 as substrates. The phosphorylated GST-ATF2 was detected after SDS-PAGE by autoradiography. UV radiation resulted in a marked increase in the activity of wild-type p38, while the mutant p38 was found to be catalytically inactive. These results show that
30 p38 is activated by dual phosphorylation within the Thr-Gly-Tyr motif.

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Example 19. MAP Kinase Phosphatase Inhibits p38 MAP
kinase Activation

The cells were treated without and with 40 J/m² UV-C. Control experiments were performed using mock-
5 transfected cells (control) and cells transfected with the catalytically inactive mutated phosphatase mPAC1 (Cys²⁵⁷/Ser) and human MKP1. The activity of p38 MAP kinase was measured with an immunocomplex protein kinase assay employing [γ -³²P]ATP and GST-ATF2 as substrates.
10 The expression of PAC1 or MKP1 was found to inhibit p38 phosphorylation, demonstrating that p38 can be regulated by the dual specificity phosphatases PAC1 and MKP1.

Example 20. Subcellular Distribution of p38 MAP Kinase

Epitope-tagged p38 MAP kinase was expressed in COS
15 cells. The cells were treated without or with 40 J/m² UV radiation and then incubated for 60 minutes at 37°C. The p38 MAP kinase was detected by indirect immunofluorescence using the M2 monoclonal antibody. The images were acquired by digital imaging microscopy and
20 processed for image restoration.

Immunocytochemistry

Coverslips (22mm x 22mm No. 1; Gold Seal Cover Glass; Becton-Dickinson) were pre-treated by boiling in 0.1 N HCl for 10 minutes, rinsed in distilled water,
25 autoclaved and coated with 0.01% poly-L-lysine (Sigma; St. Louis MO). The coverslips were placed at the bottom of 35 mm multiwell tissue culture plates (Becton Dickinson, UK). Transfected COS-1 cells were plated directly on the coverslips and allowed to adhere
30 overnight in Dulbecco's modified Eagle's medium supplemented with 5% fetal calf serum (Gibco-BRL). Twenty-four hours post-transfection, the cells were rinsed once and incubated at 37°C for 30 minutes in 25 mM Hepes, pH 7.4, 137 mM NaCl, 6 mM KCl, 1 mM MgCl₂, 1 mM

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CaCl₂, 10 mM glucose. The cells were rinsed once with phosphate-buffered saline and the coverslips removed from the tissue culture wells. Cells were fixed in fresh 4% paraformaldehyde in phosphate-buffered saline for 15 minutes at 22°C. The cells were permeabilized with 0.25% Triton® X-100 in phosphate-buffered saline for 5 minutes and washed three times in DWB solution (150 mM NaCl, 15 mM Na citrate, pH 7.0, 2% horse serum, 1% (w/v) bovine serum albumin, 0.05% Triton® X-100) for 5 minutes. The primary antibody (M2 anti-FLAG monoclonal antibody, Eastman-Kodak Co., New Haven, CT) was diluted 1:250 in DWB and applied to the cells in a humidified environment at 22°C for 1 hour. The cells were again washed three times as above and fluorescein isothiocyanate-conjugated goat anti-mouse Ig secondary antibody (Kirkegaard & Perry Laboratories Inc. Gaithersburg, MD) was applied at a 1:250 dilution for 1 hour at 22°C in a humidified environment. The cells were then washed three times in DWB and then mounted onto slides with Gel-Mount (Biomedica Corp. Foster City, CA) for immunofluorescence analysis. Control experiments were performed to assess the specificity of the observed immunofluorescence. No fluorescence was detected when the transfected cells were stained in the absence of the primary M2 monoclonal antibody, or mock-transfected cells.

Digital Imaging Microscopy and Image Restoration

Digital images of the fluorescence distribution in single cells were obtained using a Nikon 60x Planapo objective (numerical aperture = 1.4) on a Zeiss IM-35 microscope equipped for epifluorescence as previously described (Carrington et al. (1990) in: Non-invasive Techniques in Cell Biology, Fosbett & Grinstein, eds., Wiley-Liss, NY; pp. 53-72; Fay et al. (1989) J. Microsci. 153:133-149). Images of various focal planes were obtained with a computer controlled focus mechanism and a

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thermoelectrically cooled charged-coupled device camera (model 220; Photometrics Ltd., Tucson, AZ). The exposure of the sample to the excitation source was determined by a computer-controlled shutter and wavelength selector
5 system (MVI, Avon, MA). The charge-coupled device camera and microscope functions were controlled by a microcomputer, and the data acquired from the camera were transferred to a Silicon Graphics model 4D/GTX workstation (Mountainview, CA) for image processing.
10 Images were corrected for non-uniformities in sensitivity and for the dark current of the charge coupled device detector. The calibration of the microscopy blurring was determined by measuring the instrument's point spread function as a series of optical sections at $0.125\mu\text{m}$
15 intervals of a $0.3\mu\text{m}$ diameter fluorescently labeled latex bead (Molecular Probes Inc.). The image restoration algorithm used is based upon the theory of ill-posed problems and obtains quantitative dye density values within the cell that are substantially more
20 accurate than those in an unprocessed image (Carrington et al. (1990) *supra*; Fay et al. (1989) *supra*). After image processing, individual optical sections of cells were inspected and analyzed using computer graphics software on a Silicon Graphics workstation. p38 MAP
25 kinase was observed at the cell surface, in the cytoplasm, and in the nucleus. After irradiation, an increased localization of cytoplasmic p38 to the perinuclear region was detected.

Example 21. Activation of the MKK Signal Transduction
30 Pathway by Osmotic Shock

CHO cells were co-transfected with the plasmid pCMV-Flag-Jnk1 and pRSV-Neo (Dérjard et al. (1994) *supra*). A stable cell line expressing epitope-tagged Jnk1 (Flag; Immunex Corp.) was isolated by selection with

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Geneticin (Gibco-BRL). The cells were incubated with 0, 100, 150, 300, 600, or 1000 mM sorbitol for 1 hour at 37°C. The cells were collected in lysis buffer (20 mM Tris, pH 7.4, 1% TRITON® X-100, 2 mM EDTA, 137 mM NaCl, 25 mM β -glycerophosphate, 1 mM orthovanadate, 2 mM pyrophosphate, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, 10 μ g/ml leupeptin) and a soluble extract was obtained by centrifugation at 100,000 g for 30 minutes at 4°C. The epitope-tagged JNK1 was isolated by immunoprecipitation with the monoclonal antibody M2 (Immunex Corp.). The immunoprecipitates were washed extensively with lysis buffer. Immunocomplex kinase assays were done in 25 μ l of 25 mM Hepes, pH 7.4, 25 mM $MgCl_2$, 25 mM β -glycerophosphate, 2 mM dithiothreitol, 100 μ M orthovanadate, and 50 μ M ATP [γ - ^{32}P] (10 Ci/mmol) with 2.5 μ g of bacterially expressed c-Jun (residues 1-79) fused to glutathione-S-transferase (GST) as a substrate. The phosphorylation of c-Jun was examined after SDS-PAGE by autoradiography and PhosphorImager (Molecular Dynamics Inc.) analysis. JNK1 activation was observed at all concentrations of sorbitol exposure.

The time course of JNK1 protein kinase activation was measured in cells incubated in medium supplemented with 300 mM sorbitol as described above. Increased JNK1 activity was observed within 5 minutes of exposure to sorbitol, with maximum activity occurring after 15-30 minutes.

Mutation of JNK1 at the phosphorylation sites Thr¹⁸³ and Tyr¹⁸⁵ blocked the activation of JNK1 protein kinase activity by osmotic shock. CHO cells were transfected with vector, wild-type JNK1 (Thr¹⁸³, Tyr¹⁸⁵), and mutated JNK1 (Ala¹⁸³, Phe¹⁸⁵). The cells were incubated in medium supplemented without or with 300 mM sorbitol for 15 minutes before measurement of JNK1 protein kinase

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activity as described above. JNK1 activation was seen in the wild-type but not mutated JNK1.

Example 22. Molecular Cloning of MKK7

RT-PCR was employed to identify a fragment of a
5 novel mammalian MAP kinase kinase. The primers designed
for the protocol, ATNGCNGTNAARCARATG (SEQ ID NO:23) and
ATNCKYTCNGGNGCCATRTA (SEQ ID NO:24), were based on the
sequence of the Drosophila MAP kinase kinase hep (Glise
et al. (1995) Cell 83:451-461). Murine testis mRNA was
10 used as the template. A single product (461 bp) was
detected following RT-PCR amplification of murine testis
mRNA. Sequence analysis identified this PCR product as a
fragment of a novel mammalian MAP kinase kinase. Full-
length murine cDNA clones were isolated by screening a
15 murine testis library (Stratagene Inc.). The cDNA
clones were examined by sequencing with an Applied
Biosystems model 373A machine. A group of seven clones
was identified by sequence analysis to contain a single
long open reading frame that encoded a putative protein
20 kinase (Fig. 9 and Fig. 10; SEQ ID NO:17 and SEQ ID
NO:18). In-frame termination codons were detected in the
5' and 3' regions of these clones. This sequence
includes protein kinase sub-domains I - XI and is related
to the MAP kinase kinase group. The novel protein kinase
25 was designated MKK7. The sites of activating
phosphorylation of MAP kinase kinases located in sub-
domain VIII are conserved in MKK7. Comparison of MKK7
with other members of the mammalian MAP kinase kinase
group demonstrates that MKK7 is related to the JNK
30 activator MKK4. One additional cDNA clone isolated from
the λ phage library differed from the other seven clones.
This clone contained the same 3' untranslated region and
coding region of MKK7, but had a different 5' region that
lacked an in-frame termination codon. This clone

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represents an alternatively spliced form of MKK7 (MKK7b; Fig. 11; SEQ ID NO:19). The MKK7b cDNA clone does not have an initiation codon in the alternative 5' region; this cDNA therefore encodes the same MKK7 protein kinase as the other clones that were isolated. However, if the MKK7b cDNA clone is not full-length it is possible that additional 5' sequence may include an in-frame initiation codon. If true, MKK7b is predicted to fuse the sequence M-[?]-SPAPAPSQRAALQLPLANDGGSRSPPSESSPQHPTPPTRPRH- (SEQ ID NO:33) to the initiating methionine of MKK7 (Fig. 9). Although the *Drosophila* MAP kinase kinase *hep* shares substantial sequence similarity with MKK7, the sequence of the NH2-terminal extension of MKK7b is not conserved in the *hep* protein kinase. Three additional clones encoded MKK7 splice variants that differ in the 5' and 3' regions. These clones (MKK7c (Fig. 13), MKK7d (Fig. 14), and MKK7e (Fig. 15)) are full-length because of the presence of in-frame termination codons in the 5' and 3' regions.

A human cDNA library was screened with a full-length mouse MKK7 cDNA probe. A single clone was identified and sequenced. A partial MKK7 sequence was identified (Fig. 12; SEQ ID NO:25 and SEQ ID NO:26) that is missing the 3' end. The sequence is most homologous to mouse MKK7c.

The sequences of MKK7, MKK7b, *hep*, and human MKK7 cDNAs have been deposited in Genbank with accession numbers U93030, U93031, U93032, and AF00319 respectively.

Example 23. Expression of MKK7

MKK7 expression was examined by Northern blot analysis of mRNA isolated from different tissues. The analysis was done with poly A+ mRNA (2 μ g) isolated from different tissues and fractionated by denaturing agarose gel electrophoresis and transferred to a nylon membrane

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(Clontech). The blot was probed with MKK4 and MKK7 cDNAs labeled by random priming with [α - 32 P]dATP (Amersham International PLC).

MKK7 was found to be widely expressed in murine
5 tissues. A single MKK7 transcript (approximately 4.0-kb) was detected in all of the tissues examined, except for testis where two MKK7 transcripts (4.0 kb and 1.6 kb) were detected. The highest levels of MKK7 expression were in testis. Significant expression of MKK7 was also
10 observed in heart, brain, lung, liver, and kidney. This contrasts with MKK4 expression which was highest in brain although significant amounts of expression were observed in brain, liver, muscle, heart, and kidney. Although MKK4 and MKK7 are co-expressed, the relative abundance of
15 each MAP kinase kinase is different in each of the tissues examined.

Example 24. Specific Activation of JNK by MKK7 in vitro

To examine the specificity of MKK7, *in vitro* protein kinase assays were performed. A bacterial MKK7
20 expression vector was prepared by sub-cloning an MKK7 cDNA (*Eco* RI and *Pvu* II fragment) into the *Eco* RI and *Sma* I sites of pGEX-5X1 (Pharmacia-LKB). The glutathione-S-transferase (GST) fusion protein was purified by affinity chromatography (Smith and Johnson (1988) *Gene* 67:31-40).
25 The recombinant proteins GST-ATF2 (Gupta et al. (1995) *Science* 267:389-393), GST-cJun (Dérillard (1994) *supra*), GST-cMyc (Alvarez et al. (1991) *J. Biol. Chem.* 266:15277-15285), GST-ERK2 (Seth et al. (1992) *J. Biol. Chem.* 267:24796-24804), GST-p38, (Raingeaud et al. (1995) *J. Biol. Chem.* 270:7420-7426), and GST-JNK1 (Dérillard (1994) *supra*) have been described.

Protein kinase assays were performed in kinase buffer (25 mM 4-(2-hydroxyethyl)-1--
piperazineethansulfonic acid (pH 7.4), 25 mM β -
35 glycerophosphate, 25 mM $MgCl_2$, 2 mM dithiothreitol, 0.1 mM

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orthovanadate). The assays were initiated by the addition of 1 μ g of substrate proteins and 50 μ M [γ -³²P]ATP (10 Ci/mmol) in a final volume of 25 μ l. The reactions were terminated after 30 minutes at 25°C by
5 addition of Laemmli sample buffer. The phosphorylation of the substrate proteins was examined after SDS-polyacrylamide gel electrophoresis (PAGE) by autoradiography.

Recombinant MAP kinases were incubated with GST
10 (control) or GST-MKK7 using the substrate ATP [γ -³²P]. Recombinant MKK7 purified from bacteria was not observed to autophosphorylate. Incubation of the recombinant MKK7 with MAP kinases demonstrated that MKK7 phosphorylated JNK1, but not p38 or ERK2. MKK7 was phosphorylated by
15 p38 and JNK1. The significance of the retrophosphorylation of the MAP kinase kinase by the MAP kinase is unclear, but similar retrophosphorylation has been detected in kinase assays using MKK4 (Dérizard (1995) *supra*) and the Drosophila JNK activator hep (Sluss
20 (1996) *supra*).

To test whether the phosphorylation of JNK1 by MKK7 caused increased protein kinase activity, experiments using ATF2 as the JNK substrate were performed. GST-MKK7 was incubated in a protein kinase
25 assay with recombinant JNK1. JNK activity was measured by including the JNK substrate ATF2 in each assay. ATF2 was not phosphorylated by MKK7, but was weakly phosphorylated by JNK1. Incubation of MKK7 with JNK1 caused phosphorylation of JNK1 and a large increase in
30 ATF2 phosphorylation. These data indicate that MKK7 phosphorylates and activates JNK1. To confirm this conclusion, the effect of replacement of the JNK dual phosphorylation motif Thr-Pro-Tyr with Ala-Pro-Phe was examined. MKK7 did not phosphorylate the mutated JNK1
35 (APF) protein. Furthermore, MKK7 did not increase ATF2

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phosphorylation by the mutated JNK1 protein kinase.
Thus, MKK7 is a JNK activator *in vitro*.

Example 25. Specific Activation of JNK by MKK7 *in vivo*

To examine the specificity of MKK7 *in vivo*,
5 cotransfection assays were performed. CHO cells were maintained in Dulbecco's modified Eagle's medium supplemented with fetal calf serum (5%; Gibco-BRL). The cells were transfected with the lipofectamine reagent according to the manufacturer's recommendations (Gibco-
10 BRL) (Dérillard (1994) *supra*). Cells were co-transfected with vectors encoding epitope-tagged JNK1 together with an empty expression vector (control) or an expression vector encoding MKK4 or MKK7. The epitope tag was derived from the hemagglutinin protein (HA) of the
15 influenza virus. JNK1 was isolated by immunoprecipitation of cell lysates. The cells were solubilized with lysis buffer (20 mM Tris (pH 7.4), 1% TRITON X-100®, 10% glycerol, 137 mM NaCl, 2 mM EDTA, 25 mM β -glycerophosphate, 1 mM Na orthovanadate, 2 mM
20 pyrophosphate, 1 mM PMSF, 10 μ g/ml leupeptin) and centrifuged at 100,000 X g for 15 minutes at 4°C. The epitope-tagged protein kinases were immunoprecipitated by incubation for 3 hours at 4°C with an anti-HA monoclonal antibody bound to protein-G Sepharose (Pharmacia-LKB
25 Biotechnology Inc.). The immunoprecipitates were washed three times with lysis buffer (Gupta et al. (1995) Science 267:389-393). Protein kinase activity was measured in the immunocomplex with [γ -³²P]ATP and c-Jun as substrates. The product of the phosphorylation reaction
30 was visualized after SDS-PAGE by autoradiography. The ERK2 and p38 MAP kinases were not activated by co-expressed MKK7. Control experiments demonstrated that the ERK2 and p38 MAP kinases were activated by their respective cognate MAP kinase kinases, MKK1 and MKK6. In

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contrast, MKK7 did activate JNK1. Interestingly, the activation of JNK1 by co-expressed MKK7 was greater than that caused by the previously described JNK activator MKK4. Together, these data establish that MKK7 can
5 function as a specific activator of JNK in cultured cells.

Example 26. Activation of the JNK Signal Transduction Pathway by MKK7

The JNK signaling pathway is known to regulate AP-
10 1 transcriptional activity (Whitmarsh (1996) *supra*). To test the hypothesis that the expression of MKK7 would cause increased AP-1 transcriptional activity, a co-transfection assay was employed using a luciferase reporter gene that contains three AP-1 sites cloned
15 upstream of a minimal promoter element (Rincon and Flavell (1994) EMBO J. 13:4370-4381). Luciferase reporter gene expression was measured in co-transfection assays using the 0.5 μ g of the reporter plasmid pTRE-luciferase (Rincon (1994) *supra*) and 0.25 μ g of the β -
20 galactosidase expression vector pCH110 (Pharmacia-LKB). Experiments using GAL4 fusion proteins were performed using 0.25 μ g of pGAL4-ATF2 (residues 1-109), 0.5 μ g of the reporter plasmid pG5E1bLuc, and 0.25 μ g of pCH110 (Gupta et al. (1995) *supra*). The effect of protein
25 kinases was examined by co-transfection with 0.3 μ g of an empty expression vector or a protein kinase expression vector. The ERK2, p38, JNK1, MKK1, MKK3, MKK4, and MKK6 expression vectors have been described. The cells were harvested 36 hours post-transfection. The β -
30 galactosidase and luciferase activity in the cell lysates was measured as described (Gupta (1995) *supra*). Expression of MKK4, MKK7, or JNK1 did not cause marked changes in AP-1 reporter gene expression (Fig. 16A). In contrast, co-expression of MKK7 with JNK1 caused

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increased AP-1-dependent reporter gene expression. Consistent with the observation that MKK4 causes weaker activation of JNK than MKK7, co-expression of MKK4 with JNK caused a smaller increase in AP-1 reporter gene
5 expression (Fig. 16A). Together, these data demonstrate that MKK7 can function as an activator of the JNK signal transduction pathway.

To further examine the effect of MKK7 on transcriptional activity, the effect of MKK7 on the
10 transcription factor ATF2 was investigated. Previous studies have demonstrated that ATF2 is a target of the JNK signal transduction pathway (van Dam et al. (1995) *supra*; Gupta et al. (1995) *supra*; Livingstone et al (1995) *supra*). JNK phosphorylates two sites (Thr-69 and
15 Thr-71) in the NH₂-terminal activation domain of ATF2 and increases transcriptional activity. A GAL4 fusion protein strategy was employed to monitor the transcriptional activity of the activation domain of ATF2 (Gupta (1995) *supra*). Measurement of reporter gene
20 expression demonstrated that the coexpression of MKK4 with JNK1 caused increased transcriptional activity (Fig. 16B). A similar level of reporter gene expression was caused by expression of MKK7 and a larger increase was detected when MKK7 was co-expressed with JNK1. The more
25 potent effect of MKK7, compared with MKK4, on transcriptional activity is consistent with the relative effects of MKK7 and MKK4 on JNK activation. To confirm that the increased reporter gene expression was mediated by ATF2 phosphorylation, the effect of replacement of the
30 sites of ATF2 phosphorylation (Thr-69 and Thr-71) with Ala was examined. The mutated ATF2 protein was not regulated by MKK4, MKK7, or JNK1 (Fig. 16B). Together, these data demonstrate that MKK7 can regulate a physiological target of the JNK signaling pathway.

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Use

The MKK polypeptides and polynucleotides of the invention are useful for identifying reagents that modulate the MKK signal transduction pathways. Reagents that modulate an MKK signal transduction pathway can be identified by their effect on MKK synthesis, MKK phosphorylation, or MKK activity. For example, the effect of a reagent on MKK activity can be measured by the *in vitro* kinase assays described above. MKK is incubated without (control) and with a test reagent under conditions sufficient to allow the components to react, then the effect of the test reagent on kinase activity is subsequently measured. Reagents that inhibit an MKK signal transduction pathway can be used in the treatment of MKK-mediated disorders. Reagents that stimulate an MKK signal transduction pathway can be used in a number of ways, including induction of programmed cell death (apoptosis) in tissues. For example, the elimination of UV damaged cells can be used to prevent cancer.

Generally, for identification of a reagent that inhibits the MKK signal transduction pathway, a kinase assay (see, for example, Example 3) is used. A range of reagent concentrations (e.g., 1.0 nM to 100 mM) are added to a test system that includes an MKK substrate and a radioactive marker such as [γ - 32 P]ATP. Appropriate substrate molecules include p38, JNK1, JNK2, or ATF2. The incorporation of labelled phosphorus (e.g., [32]P or [33]P) into the substrate is determined, and the results obtained with the test reagent compared to control values. Of particular interest are reagents that result in inhibition of [32]P incorporation of about 80% or more. Phosphorylation may also be examined using a reagent that is phosphorylation-dependent, for example, an antibody. Phosphorylation-dependent antibodies may be made using MKK7 phosphorylated on the activating sites, Ser¹⁹⁸ and

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Thr²⁰². This may be accomplished by immunizing animals with a synthetic peptide (for example, approximately 15 amino acids in length) corresponding to the MKK7 sequence with phosphorylated Ser¹⁹⁸ and Thr²⁰². Methods of producing
5 such antibodies are known in the art. Such antibodies are useful for the detection of activated MKK7 in tissues and cell extracts (e.g. on Western blots) and may be used in a kit.

Assays that test the effect of a reagent on MKK
10 synthesis can also be used to identify compounds that inhibit MKK signal transduction pathways. The effect of the test reagent on MKK expression is measured by, for example, Western blot analysis with an antibody specific for an MKK. Antibody binding is visualized by
15 autoradiography or chemiluminescence, and is quantitated. The effect of the test reagent on MKK mRNA expression can be examined, for example, by Northern blot analysis using a polynucleotide probe or by polymerase chain reaction.

Reagents found to inhibit MKK signal transduction
20 pathways can be used as therapeutic agents for the treatment of MKK-mediated disorders. Such reagents are also useful in drug design for elucidation of the specific molecular features needed to inhibit MKK signal transduction pathways.

25 In addition, the invention provides a method for the treatment of MKK-mediated stress-related and inflammatory disorders. The method includes administration of an effective amount of a therapeutic reagent that inhibits MKK function. Suitable reagents
30 inhibit either MKK activity or expression. The concentration of the reagent to be administered is determined based on a number of factors, including the appropriate dosage, the route of administration, and the specific condition being treated. The appropriate dose
35 of a reagent is determined by methods known to those

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skilled in the art including routine experimentation to optimize the dosage as necessary for the individual patient and specific MKK-mediated disorder being treated. Specific therapeutically effective amounts appropriate
5 for administration are readily determined by one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences. 18th ed., Gennaro, ed., Mack Publishing Company, Easton, PA, 1990). Dosages may range from about 0.1-10 mg/kilo/day.

10 The invention provides methods for both acute and prophylactic treatment of stress-related and inflammatory disorders. For example, it is envisioned that ischemic heart disease will be treated during episodes of ischemia and oxidative stress following reperfusion. In addition,
15 a patient at risk for ischemia can be treated prior to ischemic episodes.

In another example, a therapeutic agent that inhibits MKK function or activity is administered to control inflammatory responses by inhibiting the
20 secretion of inflammatory cytokines, including TNF and IL-1.

Stress-related proliferative disorders can also be treated by the method of the invention by administering a therapeutic reagent that inhibits MKK function or
25 activity. Such therapeutic reagents can be used alone or in combination with other therapeutic reagents, for example, with chemotherapeutic agents in the treatment of malignancies. Indeed, the control of stress-activated MKK by the therapeutic reagents provided by this
30 invention can modulate symptoms caused by other therapeutic strategies that induce stress.

The therapeutic reagents employed are compounds which inhibit MKK function or activity, including polynucleotides, polypeptides, and other molecules such
35 as antisense oligonucleotides and ribozymes, which can be

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made according to the invention and techniques known to the art. Polyclonal or monoclonal antibodies (including fragments or derivatives thereof) that bind epitopes of MKK also can be employed as therapeutic reagents.

5 Dominant-negative forms of MKK which effectively displace or compete with MKK for substrate binding and/or phosphorylation can be used to decrease protein kinase activity. Dominant-negative forms can be created by mutations within the catalytic domain of the protein
10 kinases, using methods known in the art, and as described above (Example 13). The catalytic residues are conserved in all the MKK isoforms. For example, mutation of Lys⁷⁶ inhibits MKK7 activity. Similarly, mutation of the conserved sites of activating phosphorylation (Ser¹⁹⁸,
15 Thr²²²) inhibits MKK7 activity. These kinase-inactive forms of MKK7 act as dominant-negative inhibitors.

In some cases, augmentation of MKK activity is desirable, e.g., induction of apoptosis. The methods of the invention can be used to identify reagents capable of
20 increasing MKK function or activity. Alternatively, increased activity is achieved by over-expression of MKK. When an MKK-mediated disorder is associated with under-expression of MKK, or expression of a mutant MKK polypeptide, a sense polynucleotide sequence (the DNA
25 coding strand) or MKK polypeptide can be introduced into the cell to enhance normal MKK activity. If necessary, these treatments are targeted to specific cells by their mode of administration (e.g., by use of cell-type specific viral vectors), or by placing MKK7 nucleic acids
30 in recombinant constructs with cell-type specific or inducible promoters by methods known in the art. For example, MKK7 nucleic acid-containing vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or
35 others known in the art, used for replication and

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expression in mammalian cells. Expression of the sequence encoding the MKK7 nucleic acid can be by any promoter known in the art to act in mammalian, preferably human cells. Such promoters can be inducible or
5 constitutive. Such promoters include, but are not limited to: the SV40 early promoter region (Bernoist et al., *Nature* 290:304, 1981); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797, 1988); the herpes
10 thymidine kinase promoter (Wagner et al., *Proc. Natl. Acad. Sci. USA* 78:1441, 1981); or the regulatory sequences of the metallothionein gene (Brinster et al., *Nature* 296:39, 1988).

The antibodies of the invention can be
15 administered parenterally by injection or by gradual infusion over time. The monoclonal antibodies of the invention can be administered intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally.

20 Preparations for parenteral administration of a polypeptide or an antibody of the invention include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils
25 such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose,
30 dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose) and the like. Preservatives and other additives can also be present, such as, for

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example, antimicrobials, antioxidants, chelating agents, and inert gases, and the like.

Polynucleotide sequences, including antisense sequences, can be therapeutically administered by various techniques known to those skilled in the art. Such therapy would achieve its therapeutic effect by introduction of the MKK polynucleotide into cells of mammals having a MKK-mediated disorder. Delivery of MKK polynucleotides can be achieved using free polynucleotide or a recombinant expression vector such as a chimeric virus or a colloidal dispersion system. Especially preferred for therapeutic delivery of nucleotide sequences is the use of targeted liposomes.

Targeting of the therapeutic reagent to specific tissues is desirable to increase the efficiency of delivery. The targeting can be achieved by passive mechanisms via the route of administration. Active targeting to specific tissues can also be employed. The use of liposomes, colloidal suspensions, and viral vectors allows targeting to specific tissues by changing the composition of the formulation containing the therapeutic reagent, for example, by including molecules that act as receptors for components of the target tissues. Examples include sugars, glycolipids, polynucleotides, or proteins. These molecules can be included with the therapeutic reagent. Alternatively, these molecules can be included by indirect methods, for example, by inclusion of a polynucleotide that encodes the molecule, or by use of packaging systems that provide targeting molecules. Those skilled in the art will know, or will ascertain with the use of the teaching provided herein, which molecules and procedures will be useful for delivery of the therapeutic reagent to specific tissues.

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Transgenic animals

MKK polypeptides can also be expressed in transgenic animals. These animals represent a model system for the study of disorders that are caused by or exacerbated by overexpression or underexpression of MKK, and for the development of therapeutic agents that modulate the expression or activity of MKK. For example, dominant-negative and constitutively activated alleles could be expressed in mice to establish physiological function.

Transgenic animals can be farm animals (pigs, goats, sheep, cows, horses, rabbits, and the like) rodents (such as rats, guinea pigs, and mice), non-human primates (for example, baboons, monkeys, and chimpanzees), and domestic animals (for example, dogs and cats). Transgenic mice are especially preferred.

Any technique known in the art can be used to introduce a MKK transgene into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (U.S. Pat. No. 4,873,191); retrovirus mediated gene transfer into germ lines (Van der Putten et al., *Proc. Natl. Acad. Sci., USA* 82:6148, 1985); gene targeting into embryonic stem cells (Thompson et al., *Cell* 56:313, 1989); and electroporation of embryos (Lo, *Mol. Cell. Biol.* 3:1803, 1983). Especially useful are the methods described in Yang et al. (*Proc. Natl. Acad. Sci. USA* 94:3004-3009, 1997).

The present invention provides for transgenic animals that carry the MKK transgene in all their cells, as well as animals that carry the transgene in some, but not all of their cells. That is, the invention provides for mosaic animals. The transgene can be integrated as a single transgene or in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene can also

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be selectively introduced into and activated in a particular cell type (Lasko et al., *Proc. Natl. Acad. Sci. USA* 89:6232, 1992). The regulatory sequences required for such a cell-type specific activation will
5 depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

When it is desired that the MKK transgene be integrated into the chromosomal site of the endogenous MKK gene, gene targeting is preferred. Briefly, when
10 such a technique is to be used, vectors containing some nucleotide sequences homologous to an endogenous MKK gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of
15 the endogenous gene. The transgene also can be selectively introduced into a particular cell type, thus inactivating the endogenous MKK gene in only that cell type (Gu et al., *Science* 265:103, 1984). The regulatory sequences required for such a cell-type specific
20 inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. These techniques are useful for preparing "knock outs" having no functional MKK gene.

Once transgenic animals have been generated, the
25 expression of the recombinant MKK gene can be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to determine whether integration of the transgene has taken place. The level of mRNA expression of the
30 transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and RT-PCR. Samples of MKK gene-expressing tissue can

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also be evaluated immunocytochemically using antibodies specific for the MKK transgene product.

For a review of techniques that can be used to generate and assess transgenic animals, skilled artisans
5 can consult Gordon (*Intl. Rev. Cytol.* 115:171-229, 1989), and may obtain additional guidance from, for example: Hogan et al. Manipulating the Mouse Embryo, Cold Spring Harbor Press, Cold Spring Harbor, NY, 1986);, Krimpenfort et al. (*Bio/Technology* 9:86, 1991), Palmiter et al. (*Cell*
10 41:343, 1985), Kraemer et al. (Genetic Manipulation of the Early Mammalian Embryo, Cold Spring Harbor Press, Cold Spring Harbor, NY, 1985), Hammer et al. (*Nature* 315:680, 1985), Purcel et al. (*Science*, 244:1281, 1986), Wagner et al. (U.S. Patent No. 5,175,385), and
15 Krimpenfort et al. (U.S. Patent No. 5,175,384) (the latter two publications are hereby incorporated by reference).

Other Embodiments

It is to be understood that while the invention
20 has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are
25 within the scope of the following claims.

CLAIMS

1. A substantially pure mammalian mitogen-activated protein kinase kinase (MKK7) polypeptide having
5 serine, threonine, and tyrosine kinase activity, and phosphorylating mitogen-activated protein (MAP) kinase JNK, but not p38.

2. A polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:18, SEQ ID NO:20, SEQ ID
10 NO:26, SEQ ID NO:28, SEQ ID NO:30, or SEQ ID NO:32.

3. An isolated polynucleotide sequence encoding a polypeptide of claim 1.

4. An isolated polynucleotide sequence of claim 3 comprising the sequence of SEQ ID NO:17, SEQ ID NO:19,
15 SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, or SEQ ID NO:31, or degenerate variants thereof, or a polynucleotide sequence fully complementary to the sequence of SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, or SEQ ID NO:31, or degenerate
20 variants thereof.

5. An isolated polynucleotide sequence of claim 3 comprising a polynucleotide sequence that hybridizes under stringent hybridization conditions to the sequence of SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:25, SEQ ID
25 NO:27, SEQ ID NO:29, SEQ ID NO:31, or a complement thereof.

6. A recombinant expression vector containing a polynucleotide sequence of claim 3.

7. A recombinant host cell comprising a
30 polynucleotide sequence of claim 3.

8. A purified antibody that binds specifically to a polypeptide of claim 1.

9. A purified antibody that binds specifically to a polypeptide of claim 2.

5 10. A method of measuring the activity of a mitogen-activated protein kinase kinase (MKK7) in a biological test sample, said method comprising:

a) incubating said test sample with an MKK substrate for the MKK polypeptide of claim 1 and labeled
10 phosphate under conditions sufficient to allow phosphorylation of said substrate; and

b) determining the rate of incorporation of labeled phosphate into said substrate, wherein said rate of incorporation is a measure of MKK7 activity.

15 11. A method of claim 10, wherein said MKK substrate is selected from the group consisting of JNK MAP kinases, activating transcription factor-2 (ATF2), ATFa, cAMP response element binding protein (CRE-BPa), and c-Jun.

20 12. A method of claim 10, wherein said biological test sample is fluid, cells, or tissue obtained from a mammal.

25 13. A method for measuring the synthesis of MKK7 in a biological test sample, the method comprising the steps of:

a) obtaining a biological sample;

b) contacting said biological sample with an antibody that specifically binds an MKK7 polypeptide of claim 1; and

30 c) detecting said antibody bound to MKK7 polypeptide, wherein the level of MKK7 synthesis is determined by the amount of bound antibody.

14. A method for measuring the level of expression of MKK7 in a test sample, the method comprising the steps of:

- 5 a) isolating total or polyadenylated RNA from the test sample;
- b) incubating the RNA with a polynucleotide probe specific for an MKK7 polynucleotide of claim 3; and
- 10 c) determining the amount of said probe hybridized to the RNA, wherein the level of expression of MKK7 is directly related to the amount of MKK7 probe hybridized to the RNA.

15. A method for identifying a reagent that modulates MKK7 activity, said method comprising:

- a) obtaining a test sample containing MKK7;
- 15 b) incubating said test sample with an MKK substrate for the MKK polypeptide of claim 1, a range of reagent concentrations, and labeled phosphate under conditions sufficient to allow phosphorylation of said substrate when said reagent is not present;
- 20 c) detecting phosphorylation of said substrate; and
- d) comparing the effect of said reagent on MKK7 activity relative to a control, wherein any variation compared to control indicates a reagent able to modulate
- 25 MKK7 substrate phosphorylation.

16. A method of claim 15, wherein said MKK7 substrate is one or more of JNK, ATF2, ATFa, CRE-BPa, and c-Jun.

17. A method of claim 15 wherein said modulation
30 is inhibition of MKK7 activity.

18. A method for identifying a reagent that modulates MKK7 synthesis, said method comprising:

- a) providing a sample capable of MKK7 synthesis;

b) incubating said sample with a range of reagent concentrations under conditions that allow synthesis of MKK7 when said reagent is not present;

c) detecting an MKK7 polypeptide of claim 1; and

5 d) comparing the effect of said reagent on MKK7 synthesis relative to a control, wherein any variation compared to control indicates a reagent able to modulate MKK7.

10 19. A method of claim 18 wherein said modulation is inhibition of MKK7 synthesis.

20. A method for identifying a reagent that modulates MKK7 expression, said method comprising:

a) providing a sample capable of expressing MKK7;

15 b) incubating said sample with a range of concentrations of said reagent under conditions where MKK7 is expressed in the absence of said reagent;

c) isolating total or polyadenylated RNA from the sample;

20 d) incubating the RNA with a polynucleotide probe specific for a MKK7 nucleic acid of claim 3; and

e) comparing the effect of said reagent on MKK7 RNA expression relative to a control, wherein any variation compared to control indicates a reagent able to modulate MKK7 expression.

25 21. A method of treating an MKK7-mediated disorder in a patient, the method comprising administering to the patient a therapeutically effective amount of a reagent that modulates MKK7 activity.

30 22. The method of claim 21, wherein said MKK7-mediated disorder is selected from the group consisting of ischemic heart disease, kidney failure, oxidative liver damage, respiratory distress syndrome, heat and

radiation burns, septic shock, rheumatoid arthritis, autoimmune disorders, and inflammatory diseases.

23. A method of treating an MKK7-associated disorder in a patient, comprising administering to the
5 patient a therapeutically effective amount of an MKK7 polypeptide.

24. The method of claim 23, wherein said MKK7-associated disorder is ischemic heart disease, kidney failure, oxidative liver damage, respiratory distress
10 syndrome, heat and radiation burns, septic shock, rheumatoid arthritis, autoimmune disorders, or inflammatory diseases.

MKK3	MSKPP-----APNPTPRN-----LDSRTFTIG-----DRNFEVEADD	71
MKK4	MOGKRKALKLNAN..FKSTARFTLN...GVO.PHIERLRTHSIE.SGKLK.SP-----EQHWDFT.E.	
MEK1	MPKKKP--TPIQLN.A-PDGSVAVNGTSSAETNLEALQKLEELE..EQQRKRLEAFLTKQKVG.LKD..	
MEK2	MLARRKPVLPALTIN.TIAGFPSPTEGASEANLVLDQKLEELE..EQQRKRLEAFLTKQKVG.LKD..	
PBS2	<GTPRTGNSNNS-NSGSSGGGLFANFSKYVDIKSGSLNFAKGLSL.SK.G.DFSN-----GSSSRITL.E	
Consensus		
MKK3	72 I	142
MKK4	LVTISELGRGAYGVVEKVRHAQSGTMAVKRIRATVNSQOKRLLMDLDINMRTVDCFTYTFYGFALFREG	
MEK1	.KDLG.I.....S.N.MV.KP.Q.....S.DEK...Q.....VV..SS..P.I.Q.....	
MEK2	FEK.....A.NG...F.VS.KP.LV..R.L.HLEIKPAIRNQIIRE.QV-LHECNSP.I.G...FYSD.	
PBS2	FER.....A.NG...T.VQ.RP.L...R.L.HLEIKPAIRNQIIRE.QV-LHECNSP.I.G...FYSD.	
Consensus	.EFLD...H.N..N.S.VL.KPTNV...T.EV.LELDEAKFRQI..E.EV-LHKCNSP.I.D....F.I..	
	E G G G V K H MA K L Y V FYGA G	
MKK3	143 V	213
MKK4	DVWICMELMD-TSLDKFYR---KVLDKNMTIPEDILGEIAVSIVRALEHLSKLSVIHRDVKPSNVL-INK	
MEK1	.C.....S...F...KYVYS...D--V...E...K.TLAT.K.N..KEN.KI....I....I.-LDR	
MEK2	EIS...H..GG...Q-----K.AGR...Q...KVSIAVIKGY.TY.RE.HKIM.....I.-V.S	
PBS2	EIS...H..GG...Q-----K.AGR...Q...KVSIAVL.G.AY.RE.HQIM.....I.-V.S	
Consensus	A.YM...Y..GG...IYDESSEIGG---D.PQ.AF..NAVIHG.KE.KEQHNI.....T.I.CSAN	
	CME M S D I E L L L L HRD KP N L	
MKK3	214 VII * *	284
MKK4	EGHVCMDEGISGYLVDVSAKTMDAGCKPYMAPERINP-ELNOKGYNVKSDVMSLGITMIEMAILRFPY--	
MEK1	S.NI.L.....Q...I...R.....D.-SASRQ..D.R.....LY.L.TG.....	
MEK2	R.EI.L...V.Q.I..M.NSF-V.TRS..S...LQGTG-----S.Q..I..M.LSLV...VG.Y.IPP	
PBS2	R.EI.L...V.Q.I..M.NSF-V.TRS..S...LQGTG-----S.Q..I..M.LSLV.L.VG.Y.IPP	
Consensus	Q.T.L...V.N.A.L...NI..QS.....KSLNPDRTAT.T.Q..I....LSIL...LG.Y..PP	
	G K CDFG SG L S A G YM PER Y V SD WS G E A R P	
MKK3	285 X	355
MKK4	ESWG-----TPFOOLKQVVEEPSQLPAD---R	
MEK1	PK.N-----SV.D..T...KGD...SNSEERE	
MEK2	PDAKELELMFGCQV---EGDAAETPPRPTGRPLSSYGMDSRPPMAI.EL.DYI.N..P.K..SGV---	
PBS2	PDAKELEAFGRPVVDGEGEPHSISPRPPGRPVSGHGMDSRPPMAI.EL.DYI.N..P.K..NGV---	
Consensus	.TYD-----NI.S..SAI.DG.P.R..S.---K	
	F L V P L	
MKK3	356 XI	426
MKK4	FSPEFVDFTAQCLRNPAERMSYLEMEHPFFTLHKTKTKTDIAAFVK-----KILGEDS	
MEK1	...S.IN.VNL..T.DESK.PK.K..LK...ILMYERAVEV.CY.C-----DQMPATSSPMYVD	(SEQ ID NO: 2)
MEK2	..L..Q..VNK..I.....ADLKQ..V.A.IKRSDAEV.F.GWLCSTIGLNQPSPTTHAAGV	(SEQ ID NO: 6)
PBS2	.T.D.QE.VNK..I.....ADLKM.TN.T.IKRSEVEEV.F.GWLCKTLRLNQPSTPTRTA	(SEQ ID NO: 11)
Consensus	..SDAQD.VSL..Q.I.ER.PT.AA.T..PWLKVRNQDVHNSYITERLERN...R.RGENGLSKNV>	(SEQ ID NO: 12)
	F F CL K R L H	(SEQ ID NO: 13)
		(SEQ ID NO: 34)

FIG. 1

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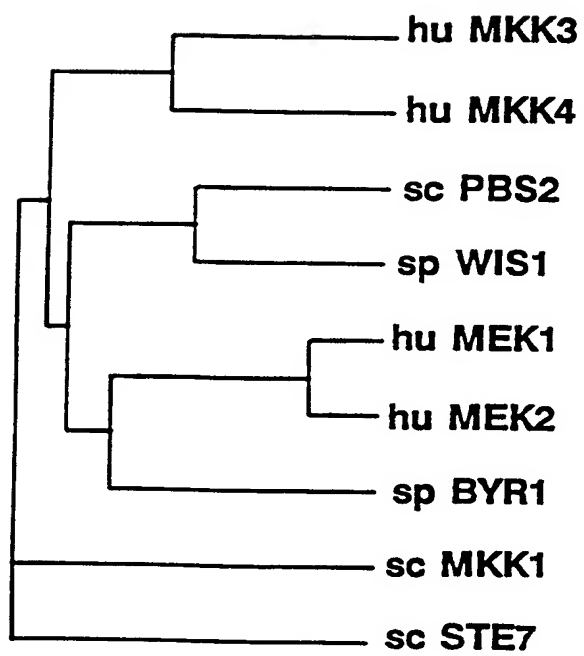
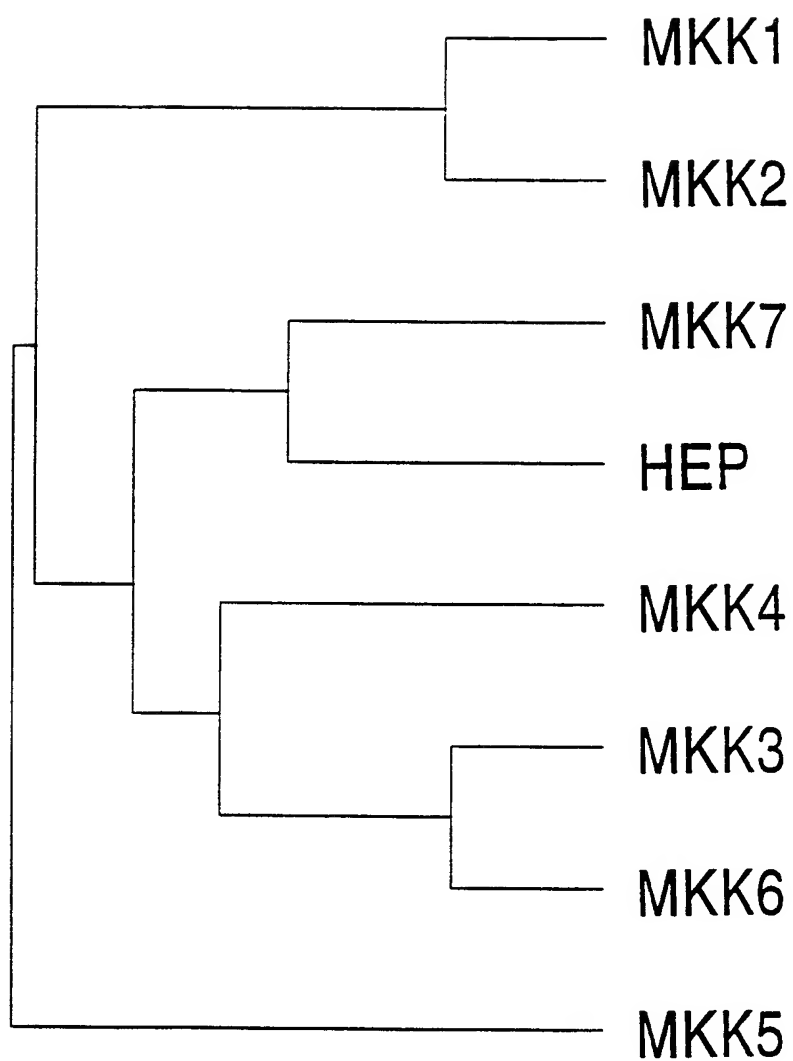
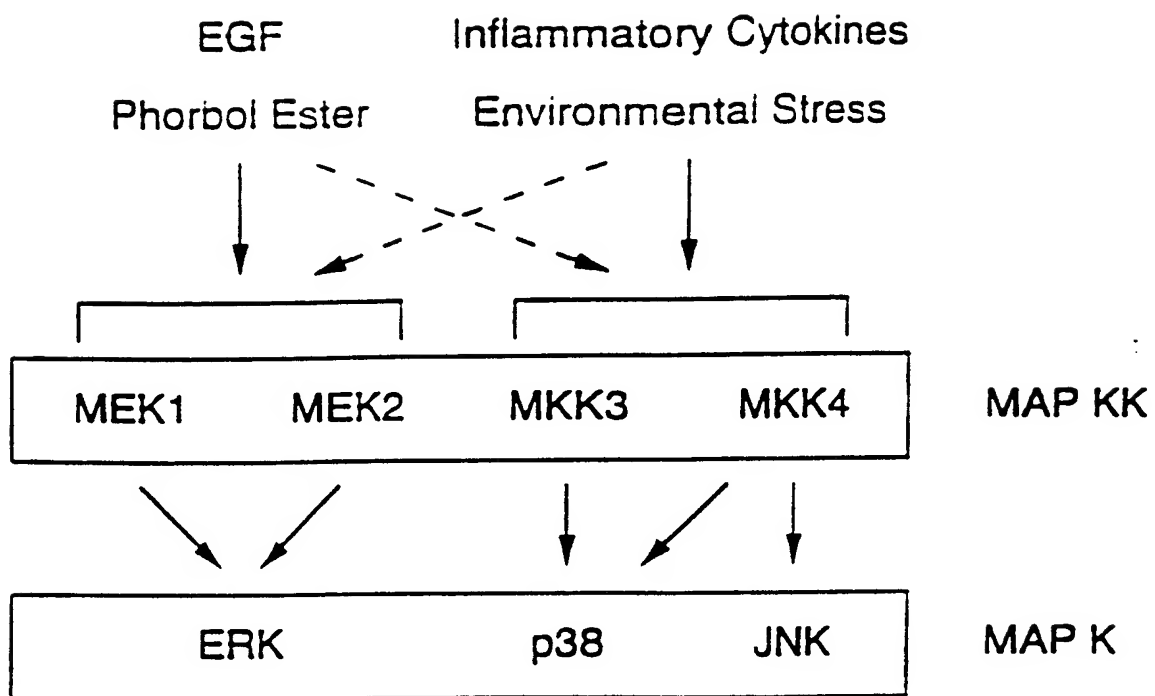


FIG. 2A

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**FIG. 2B**

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**FIG. 3**

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      5    10    15    20    25    30    35    40    45    50    55    60
      *    *    *    *    *    *    *    *    *    *    *    *
TGGCTGGCAA TGGCCTTGCT GACCTOGAGC CGGGCCCCACG TGGGGACCTT TGGAGCACAG
ACCGACCGTT ACCGGAACGA CTGGAGCTCG GCCCGGGTGC ACCCCTGGAA ACCTCGTGTC

      65    70    75    80    85    90    95   100   105   110   115   120
      *    *    *    *    *    *    *    *    *    *    *    *
CCTACGATCC TGGTGCAAGG CCGGTGGATG CAGAGGCCAG TCCATATACC ACCCAGGCCT
GGATGCTAGG ACCACGTTCC GGCCACCTAC GTCTCCGGTC AGGTATATGG TGGGTCCGGA

      125   130   135   140   145   150   155   160   165   170   175   180
      *    *    *    *    *    *    *    *    *    *    *    *
GCGAGGAGCG TGGTCCCCAC CCATCCAGCC CATATGTGCA AGTCCCCCTG ACAGAGAGGC
GGCTCCTCGC ACCAGGGGTG GGTAGGTCCG GTATACACGT TCACGGGAAC TGTCCTCCG

      185   190   195   200   205   210   215   220   225   230   235   240
      *    *    *    *    *    *    *    *    *    *    *    *
TGGTCATATC CATGGTGACC ATTTATGGGC CACAACAGGT CCCCATCTGC GCAGTGAACC
ACCAGTATAG GTACCACTCG TAAATACCCG GTGTTGTCCA GGGGTAGACG CGTCACTTGG

      245   250   255   260   265   270   275   280   285   290   295   300
      *    *    *    *    *    *    *    *    *    *    *    *
CTGTGCTGAG CACCTTGCAG ACGTGATCTT GCTTCGTCCT GCAGCACTGT GCGGGGCAGG
GACACGACTC GTGGAACGTC TGCAC TAGAA CGAAGCAGGA CGTCGTGACA CGCCCCGTCC

      305   310   315   320   325   330   335   340   345   350   355
      *    *    *    *    *    *    *    *    *    *    *
AAAATCCAAG AGGAAGAAGG ATCTACGGAT ATCCTGC ATG TCC AAG CCA CCC GCA
TTT TAGGTTT TCCTTCTTCC TAGATGCCTA TAGGACG TAC AGG TTC GGT GGG CGT
                                     Met Ser Lys Pro Pro Ala>

      360   365   370   375   380   385   390   395   400
      *    *    *    *    *    *    *    *    *
CCC AAC CCC ACA CCC CCC CGG AAC CTG GAC TCC CGG ACC TTC ATC ACC
GGG TTG GGG TGT GGG GGG GCC TTG GAC CTG AGG GCC TGG AAG TAG TGG
Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp Ser Arg Thr Phe Ile Thr>

405   410   415   420   425   430   435   440   445   450
      *    *    *    *    *    *    *    *    *    *
ATT GGA GAC AGA AAC TTT GAG GTG GAG GCT GAT GAC TTG GTG ACC ATC
TAA CCT CTG TCT TTG AAA CTC CAC CTC CGA CTA CTG AAC CAC TGG TAG
Ile Gly Asp Arg Asn Phe Glu Val Glu Ala Asp Asp Leu Val Thr Ile>

      455   460   465   470   475   480   485   490   495
      *    *    *    *    *    *    *    *    *
TCA GAA CTG GGC CGT GGA GCC TAT GGG GTG GTA GAG AAG GTG CGG CAC
AGT CTT GAC CCG GCA CCT CGG ATA CCC CAC CAT CTC TTC CAC GCC GTG
Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val Val Glu Lys Val Arg His>

500   505   510   515   520   525   530   535   540   545
      *    *    *    *    *    *    *    *    *    *
GCC CAG AGC GGC ACC ATC ATG GCC GTG AAG CGG ATC CGG GCC ACC GTG
CGG GTC TCG CCG TGG TAG TAC CGG CAC TTC GCC TAG GCC CGG TGG CAC
Ala Gln Ser Gly Thr Ile Met Ala Val Lys Arg Ile Arg Ala Thr Val>

550   555   560   565   570   575   580   585   590   595
      *    *    *    *    *    *    *    *    *    *
AAC TCA CAG GAG CAG AAG CGG CTG CTC ATG GAC CTG GAC ATC AAC ATG
TTG AGT GTC CTC GTC TTC GCC GAC GAG TAC CTG GAC CTG TAG TTG TAC
Asn Ser Gln Glu Gln Lys Arg Leu Leu Met Asp Leu Asp Ile Asn Met>

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FIG. 4A

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600	605	610	615	620	625	630	635	640							
CGC	ACG	GTC	GAC	TGT	TTC	TAC	ACT	GTC	ACC	TTC	TAC	GGG	GCA	CTA	TTC
GCG	TGC	CAG	CTG	ACA	AAG	ATG	TGA	CAG	TGG	AAG	ATG	CCC	CGT	GAT	AAG
Arg	Thr	Val	Asp	Cys	Phe	Tyr	Thr	Val	Thr	Phe	Tyr	Gly	Ala	Leu	Phe>
645	650	655	660	665	670	675	680	685	690						
AGA	GAG	GGA	GAC	GTG	TGG	ATC	TGC	ATG	GAG	CTC	ATG	GAC	ACA	TCC	TTG
TCT	CTC	CCT	CTG	CAC	ACC	TAG	ACG	TAC	CTC	GAG	TAC	CTG	TGT	AGG	AAC
Arg	Glu	Gly	Asp	Val	Trp	Ile	Cys	Met	Glu	Leu	Met	Asp	Thr	Ser	Leu>
695	700	705	710	715	720	725	730	735							
GAC	AAG	TTC	TAC	CGG	AAG	GTG	CTG	GAT	AAA	AAC	ATG	ACA	ATT	CCA	GAG
CTG	TTC	AAG	ATG	GCC	TTC	CAC	GAC	CTA	TTT	TTG	TAC	TGT	TAA	GGT	CTC
Asp	Lys	Phe	Tyr	Arg	Lys	Val	Leu	Asp	Lys	Asn	Met	Thr	Ile	Pro	Glu>
740	745	750	755	760	765	770	775	780	785						
GAC	ATC	CTT	GGG	GAG	ATT	GCT	GTG	TCT	ATC	GTG	CGG	GCC	CTG	GAG	CAT
CTG	TAG	GAA	CCC	CTC	TAA	CGA	CAC	AGA	TAG	CAC	GCC	CGG	GAC	CTC	GTA
Asp	Ile	Leu	Gly	Glu	Ile	Ala	Val	Ser	Ile	Val	Arg	Ala	Leu	Glu	His>
790	795	800	805	810	815	820	825	830	835						
CTG	CAC	AGC	AAG	CTG	TGG	GTG	ATC	CAC	AGA	GAT	GTG	AAG	CCC	TCC	AAT
GAC	GTG	TGG	TTC	GAC	AGC	CAC	TAG	GTG	TCT	CTA	CAC	TTC	GGG	AGG	TTA
Leu	His	Ser	Lys	Leu	Ser	Val	Ile	His	Arg	Asp	Val	Lys	Pro	Ser	Asn>
840	845	850	855	860	865	870	875	880							
GTC	CTT	ATC	AAC	AAG	GAG	GGC	CAT	GTG	AAG	ATG	TGT	GAC	TTT	GGC	ATC
CAG	GAA	TAG	TTG	TTC	CTC	CCG	GTA	CAC	TTC	TAC	ACA	CTG	AAA	CCG	TAG
Val	Leu	Ile	Asn	Lys	Glu	Gly	His	Val	Lys	Met	Cys	Asp	Phe	Gly	Ile>
885	890	895	900	905	910	915	920	925	930						
AGT	GGC	TAC	TTG	GTG	GAC	TCT	GTG	GCC	AAG	ACG	ATG	GAT	GCC	GGC	TGC
TCA	CCG	ATG	AAC	CAC	CTG	AGA	CAC	CGG	TTC	TGC	TAC	CTA	CCG	CCG	ACG
Ser	Gly	Tyr	Leu	Val	Asp	Ser	Val	Ala	Lys	Thr	Met	Asp	Ala	Gly	Cys>
935	940	945	950	955	960	965	970	975							
AAG	CCC	TAC	ATG	GCC	CCT	GAG	AGG	ATC	AAC	CCA	GAG	CTG	AAC	CAG	AAG
TTC	GGG	ATG	TAC	CGG	GGA	CTC	TCC	TAG	TTG	GGT	CTC	GAC	TTG	GTC	TTC
Lys	Pro	Tyr	Met	Ala	Pro	Glu	Arg	Ile	Asn	Pro	Glu	Leu	Asn	Gln	Lys>
980	985	990	995	1000	1005	1010	1015	1020	1025						
GGC	TAC	AAT	GTC	AAG	TCC	GAC	GTC	TGG	AGC	CTG	GGC	ATC	ACC	ATG	ATT
CCG	ATG	TTA	CAG	TTC	AGG	CTG	CAG	ACC	TGG	GAC	CCG	TAG	TGG	TAC	TAA
Gly	Tyr	Asn	Val	Lys	Ser	Asp	Val	Trp	Ser	Leu	Gly	Ile	Thr	Met	Ile>
1030	1035	1040	1045	1050	1055	1060	1065	1070	1075						
GAG	ATG	GCC	ATC	CTG	CGG	TTC	CCT	TAC	GAG	TCC	TGG	GGG	ACC	CCG	TTC
CTC	TAC	CGG	TAG	GAC	GCC	AAG	GGA	ATG	CTC	AGG	ACC	CCC	TGG	GGC	AAG
Glu	Met	Ala	Ile	Leu	Arg	Phe	Pro	Tyr	Glu	Ser	Trp	Gly	Thr	Pro	Phe>
1080	1085	1090	1095	1100	1105	1110	1115	1120							

FIG. 4B

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      *           *           *           *           *
CAG CAG CTG AAG CAG GTG GTG GAG GAG CCG TCC CCC CAG CTC CCA GCC
GTC GTC GAC TTC GTC CAC CAC CTC CTC GGC AGG GGG GTC GAG GGT CCG
Gln Gln Leu Lys Gln Val Val Glu Glu Pro Ser Pro Gln Leu Pro Ala>

1125   1130   1135   1140   1145   1150   1155   1160   1165   1170
      *           *           *           *           *
GAC CGT TTC TCC CCC GAG TTT GTG GAC TTC ACT GGT CAG TGC CTG AGG
CTG GCA AAG AGG GGG CTC AAA CAC CTG AAG TGA CGA GTC ACG GAC TCC
Asp Arg Phe Ser Pro Glu Phe Val Asp Phe Thr Ala Gln Cys Leu Arg>

1175   1180   1185   1190   1195   1200   1205   1210   1215
      *           *           *           *           *
AAG AAC CCC GCA GAG CGT ATG AGC TAC CTG GAG CTG ATG GAG CAC CCC
TTC TTG GGG CGT CTC GCA TAC TCG ATG GAC CTC GAC TAC CTC GTG GGG
Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu Glu Leu Met Glu His Pro>

1220   1225   1230   1235   1240   1245   1250   1255   1260   1265
      *           *           *           *           *
TTC TTC ACC TTG CAC AAA ACC AAG AAG ACG GAC ATT GGT GCC TTC GTG
AAG AAG TGG AAC GTG TTT TGG TTC TTC TGC CTG TAA CGA CCG AAG CAC
Phe Phe Thr Leu His Lys Thr Lys Lys Thr Asp Ile Ala Ala Phe Val>

1270   1275   1280   1285   1290   1295   1300   1305   1310   1315   1320
      *           *           *           *           *
AAG AAG ATC CTG GGA GAA GAC TCA TAGGGGCTG GGCCTCGGAC CCCACTCCGG
TTC TTC TAG GAC CCT CTT CTG AGT ATCCCCGAC CCGGAGCCTG GGGTGAGGCC
Lys Lys Ile Leu Gly Glu Asp Ser> (SEQ ID NO:2)

1325   1330   1335   1340   1345   1350   1355   1360   1365   1370   1375   1380
      *           *           *           *           *
CCCTCCAGAG CCCACAGCC CCATCTGCGG GGCAGTGCT CACCCACACC ATAAGCTACT
GGGAGGTCTC GGGGTGTCCG GGTAGACGCC CCCGTCACGA GTGGGTGTGG TATTCGATGA

1385   1390   1395   1400   1405   1410   1415   1420   1425   1430   1435   1440
      *           *           *           *           *
GCCATCCTGG CCCAGGGCAT CTGGGAGGAA CCGAGGGGGC TGCTCCCAAC TGGCTCTGTG
CGGTAGGACC GGGTCCCGTA GACCCTCCTT GGCTCCCCCG ACGAGGGTGG ACCGAGACAC

1445   1450   1455   1460   1465   1470   1475   1480   1485   1490   1495   1500
      *           *           *           *           *
GCGAGCCATT TGTCCCAAGT GCCAAAGAAG CAGACCATTG GGGCTCCCAAG CCAGGCCCTT
CGCTCGGTAA ACAGGGTTCA CGGTTTCTTC GTCTGGTAAC CCCGAGGGTC GGTCCGGGAA

1505   1510   1515   1520   1525   1530   1535   1540   1545   1550   1555   1560
      *           *           *           *           *
GTCGGCCCCA CCAGTGCCTC TCCCTGCTGC TCCTAGGACC CGTCTCCAGC TGCTGAGATC
CAGCCGGGGT GGTACCGGAG AGGGACGACG AGGATCCTGG GCAGAGGTGG ACGACTCTAG

1565   1570   1575   1580   1585   1590   1595   1600   1605   1610   1615   1620
      *           *           *           *           *
CTGGACTGAG GGGGCTGGA TGCCCCCTGT GGATGCTGCT GCGGCTGCAC AGCAGGCTGC
GACCTGACTC CCCCCGACCT ACGGGGGACA CCTACGACGA CGGGGACGTG TCCTCCGACG

1625   1630   1635   1640   1645   1650   1655   1660   1665   1670   1675   1680
      *           *           *           *           *
CAGTGCCTGG GTGGATGGGC CACCGCCTTG CCCAGCCTGG ATGCCATCCA AGTTGTATAT
GTCACGGACC CACCTACCCG GTGGCGGAAC GGGTCGGACC TACGGTAGGT TCAACATATA

1685   1690   1695   1700   1705   1710   1715   1720   1725   1730   1735   1740
      *           *           *           *           *
TTTTTAATC TCTCGACTGA ATGGACTTTG CACACTTTGG CCCAGGGTGG CCACACCTCT

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FIG. 4C

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AAAAAATTAG AGAGCTGACT TACCTGAAAC GTGTGAAACC GGGTCCCACC GGTGTGGAGA
1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800
ATCCCGGCTT TGGTGCGGGG TACACAAGAG GGGATGAGTT GTGTGAATAC CCCAAGACTC
TAGGGCCGAA ACCACGCCCC ATGTGTTCTC CCTACTCAA CACACTTATG GGGTCTGAG
1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860
CCATGAGGGA GATGCCATGA GCGGCCCCAG GCCTTCCCCCT GGCACCTGCA AACAGGGCCT
GGTACTCCCT CTACGGTACT CCGCGGGGTT CCGAAGGGGA CCGTGACCCT TTGTCCCAGA
1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920
CTGCGGAGCA CACTGGCTCA CCCAGTCCTG CCGCCACCG TTATCGGTGT CATTACCTT
GACGCCTCGT GTGACCGAGT GGGTCAGGAC GGGCGGTGGC AATAGCCACA GTAGTGGA
1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980
TCGTGTTTTT TTTAATTAT CCTCTGTGA TTTTCTTTT TGCTTTATGG GTTGGCTTG
AGCACAAAAA AAATTAAATA GGAGACAACT AAAAAAGAAA ACGAAATACC CAAACCGAAC
1985 1990 1995 2000 2005 2010 2015 2020 2025 2030
TTTTCTTGC ATGGTTTGGA GCTGATCGCT TCTCCCCAC CCCCTAGGGG (SEQ ID NO: 1)
AAAAAGAAG TACCAAACCT CGACTAGCGA AGAGGGGGTG GGGGATCCCC

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FIG. 4D

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      5    10    15    20    25    30    35    40    45    50    55    60
      *    *    *    *    *    *    *    *    *    *    *    *
TAGCTGCAGC ACAGCCTTCC CTAACGTTGC AACTGGGGGA AAAATCACCTT TCCAGTCGT
ATCGACGTCG TGTCCGAAGG GATTGCAACG TTGACCCCTT TTTTAGTGAA AGGTCAGACA

      65    70    75    80    85    90    95   100   105   110   115   120
      *    *    *    *    *    *    *    *    *    *    *    *
TTTGCAAGGT GTGCATTTC ATCTTGATTG CCTGAAAGTC CATCTGCTGC ATCGGTCAAG
AAACGTTCCA CACGTAAAGG TAGAACTAAG GGACTTTCAG GTAGACGACG TAGCCAGTTC

      125   130   135   140   145   150   155   160   165   170   175   180
      *    *    *    *    *    *    *    *    *    *    *    *
AGAAACTCCA CTTGCATGAA GATTGCACGC CTGCAGCTTG CATCTTTGTT GCAAAACTAG
TCTTTGAGGT GAACGTACTT CTAACGTGCG GACGTCCAAC GTAGAAACAA CGTTTTGATC

      185   190   195   200   205   210   215   220   225   230   235   240
      *    *    *    *    *    *    *    *    *    *    *    *
CTACAGAAGA GAAGCAAGGC AAAGTCTTTT GTGCTCCCTT CCCCCATCAA AGGAAAGGGG
GATGTCTTCT CTTGCTTCCG TTTCAGAAAA CACGAGGGGA GGGGGTAGTT TCTTTTCCCC

      245   250   255   260   265   270   275   280   285
      *    *    *    *    *    *    *    *    *
AAA ATG TCT CAG TCG AAA GGC AAG AAG CGA AAC CCT GGC CTT AAA ATT
TTT TAC AGA GTC AGC TTT CCG TTC TTC GCT TTG GGA CCG GAA TTT TAA
Met Ser Gln Ser Lys Gly Lys Lys Arg Asn Pro Gly Leu Lys Ile>

      290   295   300   305   310   315   320   325   330   335
      *    *    *    *    *    *    *    *    *    *
CCA AAA GAA GCA TTT GAA CAA CCT CAG ACC AGT TCC ACA CCA CCT AGA
GGT TTT CTT CGT AAA CTT GTT GGA GTC TGG TCA AGG TGT GGT GGA TCT
Pro Lys Glu Ala Phe Glu Gln Pro Gln Thr Ser Ser Thr Pro Pro Arg>

      340   345   350   355   360   365   370   375   380
      *    *    *    *    *    *    *    *    *
GAT TTA GAC TCC AAG GCT TGC ATT TCT ATT GGA AAT CAG AAC TTT GAG
CTA AAT CTG AGG TTC CGA ACG TAA AGA TAA CCT TTA GTC TTG AAA CTC
Asp Leu Asp Ser Lys Ala Cys Ile Ser Ile Gly Asn Gln Asn Phe Glu>

      385   390   395   400   405   410   415   420   425   430
      *    *    *    *    *    *    *    *    *    *
GTG AAG GCA GAT GAC CTG GAG CCT ATA ATG GAA CTG GGA CGA GGT GCG
CAC TTC CGT CTA CTG GAC CTC GGA TAT TAC CTT GAC CGT CCA CGC
Val Lys Ala Asp Asp Leu Glu Pro Ile Met Glu Leu Gly Arg Gly Ala>

      435   440   445   450   455   460   465   470   475   480
      *    *    *    *    *    *    *    *    *    *
TAC GGG GTG GTG GAG AAG ATG CGG CAC GTG CCC AGC GGG CAG ATC ATG
ATG CCC CAC CAC CTC TTC TAC GCC GTG CAC GGG TCG CCC GTC TAG TAC
Tyr Gly Val Val Glu Lys Met Arg His Val Pro Ser Gly Gln Ile Met>

      485   490   495   500   505   510   515   520   525
      *    *    *    *    *    *    *    *    *
GCA GTG AAG CGG ATC CGA GCC ACA GTA AAT AGC CAG GAA CAG AAA CGG
CGT CAC TTC GCC TAG GCT CGG TGT CAT TTA TCG GTC CTT GTC TTT GCC
Ala Val Lys Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg>

      530   535   540   545   550   555   560   565   570   575
      *    *    *    *    *    *    *    *    *    *
CTA CTG ATG GAT TTG GAT ATT TCC ATG AGG ACG GTG GAC TGT CCA TTC
GAT GAC TAG CTA AAC CTA TAA AGG TAC TCC TGC CAC CTG ACA GGT AAG

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FIG. 5A

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Leu Leu Met Asp Leu Asp Ile Ser Met Arg Thr Val Asp Cys Pro Phe>
  580   585   590   595   600   605   610   615   620
    *   *   *   *   *   *   *   *   *
ACT GTC ACC TTT TAT GGC GCA CTG TTT CGG GAG GGT GAT GTG TGG ATC
TGA CAG TGG AAA ATA CCG CGT GAC AAA GCC CTC CCA CTA CAC ACC TAG
Thr Val Thr Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile>
625   630   635   640   645   650   655   660   665   670
    *   *   *   *   *   *   *   *   *
TGC ATG GAG CTC ATG GAT ACA TCA CTA GAT AAA TTC TAC AAA CAA GTT
ACG TAC CTC GAG TAC CTA TGT AGT GAT CTA TTT AAG ATG TTT GTT CAA
Cys Met Glu Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Lys Gln Val>
675   680   685   690   695   700   705   710   715   720
    *   *   *   *   *   *   *   *   *
ATT GAT AAA GCC CAG ACA ATT CCA GAG GAC ATC TTA GGG AAA ATA GCA
TAA CTA TTT CCG GTC TGT TAA GGT CTC CTG TAG AAT CCC TTT TAT CGT
Ile Asp Lys Gly Gln Thr Ile Pro Glu Asp Ile Leu Gly Lys Ile Ala>
  725   730   735   740   745   750   755   760   765
    *   *   *   *   *   *   *   *   *
GTT TCT ATT GTA AAA GCA TTA GAA CAT TTA CAT AGT AAG CTC TCT GTC
CAA AGA TAA CAT TTT CGT AAT CTT GTA AAT GTA TCA TTC GAC AGA CAG
Val Ser Ile Val Lys Ala Leu Glu His Leu His Ser Lys Leu Ser Val>
770   775   780   785   790   795   800   805   810   815
    *   *   *   *   *   *   *   *   *
ATT CAC AGA GAC GTC AAG CCT TCT AAT GTA CTC ATC AAT GCT CTC GGT
TAA GTG TCT CTG CAG TTC GGA AGA TTA CAT GAG TAG TTA CGA GAG CCA
Ile His Arg Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly>
  820   825   830   835   840   845   850   855   860
    *   *   *   *   *   *   *   *   *
CAA GTG AAG ATG TGC GAT TTT GGA ATC AGT GGC TAC TTG GTG GAC TCT
GTT CAC TTC TAC ACG CTA AAA CCT TAG TCA CCG ATG AAC CAC CTG AGA
Gln Val Lys Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser>
865   870   875   880   885   890   895   900   905   910
    *   *   *   *   *   *   *   *   *
GTT GCT AAA ACA ATT GAT GCA GGT TGC AAA CCA TAC ATG GCC CCT GAA
CAA CGA TTT TGT TAA CTA CGT CCA ACG TTT GGT ATG TAC CGG GGA CTT
Val Ala Lys Thr Ile Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu>
  915   920   925   930   935   940   945   950   955   960
    *   *   *   *   *   *   *   *   *
AGA ATA AAC CCA GAG CTC AAC CAG AAG GGA TAC AGT GTG AAG TCT GAC
TCT TAT TTG GGT CTC GAG TTG GTC TTC CCT ATG TCA CAC TTC AGA CTG
Arg Ile Asn Pro Glu Leu Asn Gln Lys Gly Tyr Ser Val Lys Ser Asp>
  965   970   975   980   985   990   995  1000  1005
    *   *   *   *   *   *   *   *   *
ATT TGG AGT CTG GGC ATC ACG ATG ATT GAG TTG GCC ATC CTT CGA TTT
TAA ACC TCA GAC CCG TAG TGC TAC TAA CTC AAC CGG TAG GAA GCT AAA
Ile Trp Ser Leu Gly Ile Thr Met Ile Glu Leu Ala Ile Leu Arg Phe>
1010  1015  1020  1025  1030  1035  1040  1045  1050  1055
    *   *   *   *   *   *   *   *   *
CCC TAT GAT TCA TGG GGA ACT CCA TTT CAG CAG CTC AAA CAG GTG GTA
GGG ATA CTA AGT ACC CCT TGA GGT AAA GTC GTC GAG TTT GTC CAC CAT
Pro Tyr Asp Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val>

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FIG. 5B

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1060 1065 1070 1075 1080 1085 1090 1095 1100
* * * * *
GAG GAG CCA TCG CCA CAA CTC CCA GCA GAC AAG TTC TCT GCA GAG TTT
CTC CTC GGT AGC GGT GTT GAG GGT CGT CTG TTC AAG AGA CGT CTC AAA
Glu Glu Pro Ser Pro Gln Leu Pro Ala Asp Lys Phe Ser Ala Glu Phe>

1105 1110 1115 1120 1125 1130 1135 1140 1145 1150
* * * * *
GTT GAC TTT ACC TCA CAG TGC TTA AAG AAG AAT TCC AAA GAA CGG CCT
CAA CTG AAA TGG AGT GTC ACG AAT TTC TTC TTA AGG TTT CTT GCC GGA
Val Asp Phe Thr Ser Gln Cys Leu Lys Lys Asn Ser Lys Glu Arg Pro>

1155 1160 1165 1170 1175 1180 1185 1190 1195 1200
* * * * *
ACA TAC CCA GAG CTA ATG CAA CAT CCA TTT TTC ACC CTA CAT GAA TCC
TGT ATG GGT CTC GAT TAC GTT GTA GGT AAA AAG TGG GAT GTA CTT AGG
Thr Tyr Pro Glu Leu Met Gln His Pro Phe Phe Thr Leu His Glu Ser>

1205 1210 1215 1220 1225 1230 1235 1240 1245 1250
* * * * *
AAA GGA ACA GAT GTG GCA TCT TTT GTA AAA CTG ATT CTT GGA GAC TAAAA
TTT CCT TGT CTA CAC CGT AGA AAA CAT TTT GAC TAA GAA CCT CTG ATTTT
Lys Gly Thr Asp Val Ala Ser Phe Val Lys Leu Ile Leu Gly Asp> (SEQ ID NO:4)

1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310
* * * * *
AGCAGTGGAC TTAATCGGTT GACCCCTACTG TGGATTGGTG GGTTCGGGG TGAAGCAAGT
TCGTCACCTG AATTAGCCAA CTGGGATGAC ACCTAACCAC CCAAAGCCCC ACTTCGTTCA

1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370
* * * * *
TCACTACAGC ATCAATAGAA AGTCATCTTT GAGATAATTT AACCTGCCT CTCAGAGGGT
AGTGATGTCT TAGTTATCTT TCAGTAGAAA CTCTATTAAA TTGGGACGGA GAGTCCTCCA

1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430
* * * * *
TTTCTCTCCC AATTTCCTTT TTAATCCCCC TCTTAAGGGG GCCTTGGAAT CTATAGTATA
AAAGAGAGGG TTAAAGAAA AATGAGGGGG AGAATTCCCC CGGAACCTTA GATATCATAT

1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490
* * * * *
GAATGAACTG TCTAGATGGA TGAATTATGA TAAAGCCTTA GGACTTCAAA AGGTGATTAA
CTTACTTGAC AGATCTACCT ACTTAATACT ATTTCCGAAT CCTGAAGTTT TCCACTAATT

1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550
* * * * *
ATATTTAATG ATGTGTCATA TGAGTCCTCA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
TATAAATTAC TACACAGTAT ACTCAGGAGT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT

1555 1560 1565 1570 1575 1580 1585 1590 1595 1600
* * * * *
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AA (SEQ ID NO:3)
TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TT

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FIG. 5C

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      5      10      15      20      25      30      35      40      45      50      55
      *      *      *      *      *      *      *      *      *      *      *
CTAGGGTCCC CGGCGCCAGG CCACCCGGCC CTCAGCAGC ATG CAG GGT AAA CGC AAA
GATCCAGGG GCCGCGGTCC GGTGGGCCGG CAGTCGTGC TAC GTC CCA TTT GCG TTT
                               Met Gln Gly Lys Arg Lys>

      60      65      70      75      80      85      90      95      100     105
      *      *      *      *      *      *      *      *      *      *
GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC AAA TCT ACA GCA AGG
CGT GAC TTC AAC TTA AAA CGT TTA GGT GGA AAG TTT AGA TGT CGT TCC
Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe Lys Ser Thr Ala Arg>

      110     115     120     125     130     135     140     145     150
      *      *      *      *      *      *      *      *      *
TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA AAC CCA CAC ATA GAG
AAA TGA GAC TTA GGG TTA GGA TGT CCT CAA GTT TTG GGT GTG TAT CTC
Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln Asn Pro His Ile Glu>

      155     160     165     170     175     180     185     190     195     200
      *      *      *      *      *      *      *      *      *      *
AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA AAA CTG AAG ATC TCC
TCT GAC TCT TGT GTG TCG TAA CTC AGT AGT CCT TTT GAC TTC TAG AGG
Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly Lys Leu Lys Ile Ser>

      205     210     215     220     225     230     235     240     245
      *      *      *      *      *      *      *      *      *
CCT GAA CAA CAC TGG GAT TTC ACT GCA GAG GAC TTG AAA GAC CTT GGA
GGA CTT GTT GTG ACC CTA AAG TGA CGT CTC CTG AAC TTT CTG GAA CCT
Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp Leu Lys Asp Leu Gly>

      250     255     260     265     270     275     280     285     290     295
      *      *      *      *      *      *      *      *      *      *
GAA ATT CGA CGA GGA GCT TAT GGT TCT GTC AAC AAA ATG GTC CAC AAA
CTT TAA CCT GCT CCT CGA ATA CCA AGA CAG TTG TTT TAC CAG GTG TTT
Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn Lys Met Val His Lys>

      300     305     310     315     320     325     330     335     340     345
      *      *      *      *      *      *      *      *      *      *
CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT CGG TCA ACA GTG GAT
GGT TCA CCC GTT TAT TAC CGT CAA TTT TCT TAA GCC AGT TGT CAC CTA
Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile Arg Ser Thr Val Asp>

      350     355     360     365     370     375     380     385     390
      *      *      *      *      *      *      *      *      *
GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG GAT GTA GTA ATG CGG
CTT TTT CTT GTT TTT GTT GAA GAA TAC CTA AAC CTA CAT CAT TAC GCC
Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu Asp Val Val Met Arg>

      395     400     405     410     415     420     425     430     435     440
      *      *      *      *      *      *      *      *      *      *
AGT AGT GAT TGC CCA TAC ATT GTT CAG TTT TAT GGT GCA CTC TTC AGA
TCA TCA CTA ACG GGT ATG TAA CAA GTC AAA ATA CCA CGT GAG AAG TCT
Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr Gly Ala Leu Phe Arg>

      445     450     455     460     465     470     475     480     485
      *      *      *      *      *      *      *      *      *
GAG GGT GAC TGT TGG ATC TGT ATG GAA CTC ATG TCT ACC TCG TTT GAT
CTC CCA CTG ACA ACC TAG ACA TAC CTT GAG TAC AGA TGG AGC AAA CTA
Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met Ser Thr Ser Phe Asp>

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FIG. 6A

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490   495   500   505   510   515   520   525   530   535
*      *      *      *      *      *      *      *      *
AAG TTT TAC AAA TAT GTA TAT AGT GTA TTA GAT GAT GTT ATT CCA GAA
TTC AAA ATG TTT ATA CAT ATA TCA CAT AAT CTA CTA CAA TAA GGT CTT
Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp Asp Val Ile Pro Glu>

540   545   550   555   560   565   570   575   580   585
*      *      *      *      *      *      *      *      *
GAA ATT TTA GGC AAA ATC ACT TTA GCA ACT GTG AAA GCA CTA AAC CAC
CTT TAA AAT CCG TTT TAG TGA AAT CGT TGA CAC TTT CGT GAT TTG GTG
Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val Lys Ala Leu Asn His>

590   595   600   605   610   615   620   625   630
*      *      *      *      *      *      *      *
TTA AAA GAA AAC TTG AAA ATT ATT CAC AGA GAT ATC AAA CCT TCC AAT
AAT TTT CTT TTG AAC TTT TAA TAA GTG TCT CTA TAG TTT GGA AGG TTA
Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp Ile Lys Pro Ser Asn>

635   640   645   650   655   660   665   670   675   680
*      *      *      *      *      *      *      *
ATT CTT CTG GAC AGA AGT GGA AAT ATT AAG CTC TGT GAC TTC GGC ATC
TAA GAA GAC CTG TCT TCA CCT TTA TAA TTC GAG ACA CTG AAG CCG TAG
Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu Cys Asp Phe Gly Ile>

685   690   695   700   705   710   715   720   725
*      *      *      *      *      *      *
AGT GGA CAG CTT GTG GAC TCT ATT GCC AAG ACA AGA GAT GCT GGC TGT
TCA CCT GTC GAA CAC CTG AGA TAA CCG TTC TGT TCT CTA CGA CCG ACA
Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr Arg Asp Ala Gly Cys>

730   735   740   745   750   755   760   765   770   775
*      *      *      *      *      *      *      *
AGG CCA TAC ATG GCA CCT GAA AGA ATA GAC CCA AGC GCA TCA CGA CAA
TCC GGT ATG TAC CGT GGA CTT TCT TAT CTG GGT TCG CGT AGT GCT GTT
Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro Ser Ala Ser Arg Gln>

780   785   790   795   800   805   810   815   820   825
*      *      *      *      *      *      *      *
GGA TAT GAT GTC CGC TCT GAT GTC TGG AGT TTG GGG ATC ACA TTG TAT
CCT ATA CTA CAG GCG AGA CTA CAG ACC TCA AAC CCC TAG TGT AAC ATA
Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu Gly Ile Thr Leu Tyr>

830   835   840   845   850   855   860   865   870
*      *      *      *      *      *      *      *
GAG TTG GCC ACA GGC CGA TTT CCT TAT CCA AAG TGG AAT AGT GTA TTT
CTC AAC CCG TGT CCG GCT AAA GGA ATA GGT TTC ACC TTA TCA CAT AAA
Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val Phe>

875   880   885   890   895   900   905   910   915   920
*      *      *      *      *      *      *      *
GAT CAA CTA ACA CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT AAT
CTA GTT GAT TGT GTT CAG CAC TTT CCT CTA GGA GGC GTC GAC TCA TTA
Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser Asn>

925   930   935   940   945   950   955   960   965
*      *      *      *      *      *      *
TCT GAG GAA AGG GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC TTG
AGA CTC CTT TCC CTT AAG AGG GGC TCA AAG TAG TTG AAA CAG TTG AAC
Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Asn Leu>

970   975   980   985   990   995   1000  1005  1010  1015
*      *      *      *      *      *      *

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FIG. 6B

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TGC CTT ACG AAG GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT CTG
 ACG GAA TGC TTC CTA CTT AGG TTT TCC GGT TTC ATA TTT CTC GAA GAC
 Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu Leu>

1020 1025 1030 1035 1040 1045 1050 1055 1060 1065
 * * * * *
 AAA CAT CCC TTT ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC GCA
 TTT GTA GGG AAA TAA AAC TAC ATA CTT CTT GCA CGG CAA CTC CAG CGT
 Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val Ala>

1070 1075 1080 1085 1090 1095 1100 1105 1110
 * * * * *
 TGC TAT GTT TGT AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC TCT
 ACG ATA CAA ACA TTT TAG GAC CTA GTT TAC GGT CGA TGA GGG TCG AGA
 Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser Ser>

1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170
 * * * * *
 CCC ATG TAT GTC GAT TG ATATCGTTCG TACATCAGAC TCTAGAAAAA AGGGCTGAGA
 GGG TAC ATA CAG CTA AC TATAGCRACG ATGTAGTCTG AGATCTTTTT TCCCGACTCT
 Pro Met Tyr Val Asp> (SEQ ID NO:6)

1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230
 * * * * *
 GGAAGCAAGA CGTAAAGAAT TTTTCATCCCG TATCACAGTG TTTTATATGC TCGCCAGAC
 CCTTCGTTCT GCATTTCTTA AAAGTAGGGC ATAGTGTAC AAAAAATAACG AGCGGGTCTG

1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290
 * * * * *
 ACCATGTGCA ATAAGATTGG TGTTCGTTTC CATCATGTCT GTATACTCCT CTCACCTAGA
 TGGTACACGT TATTCTAACC ACAAGCAAAG GTAGTACAGA CATATGAGGA CAGTGGATCT

1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350
 * * * * *
 ACGTGCATCC TTGTAATACC TGATTGATCA CACAGTGTTA GTGCTGGTCA GAGAGACCTC
 TGCACGTAGG AACATTATGG ACTAACTAGT GTGTCACAAT CACGACCAGT CTCTCTGGAG

1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410
 * * * * *
 ATCCTGCTCT TTTGTGATGA ACATATTTCAT GAAATGTGGA AGTCAGTACG ATCAAGTTGT
 TAGGACGAGA AAACACTACT TGTATAAGTA CTTTACACCT TCAGTCATGC TAGTTCAACA

1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470
 * * * * *
 TGACTGTGAT TAGATCACAT CTTAAATTCA TTTCTAGACT CAAAACCTGG AGATGCAGCT
 ACTGACACTA ATCTAGTGTA GAATTTAAGT AAAGATCTGA GTTTTGGACC TCTACGTGCA

1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530
 * * * * *
 ACTGGAATGG TGTTTTGTCA GACTTCCAAA TCCTGGAAGG ACACAGTGAT GAATGTACTA
 TGACCTTACC ACAAACAGT CTGAAGGTTT AGGACCTTCC TGTGTCACTA CTTACATGAT

1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590
 * * * * *
 TATCTGAACA TAGAACTCG GGCTTGAGTG AGAAGAGCTT GCACAGCCAA CGAGACACAT
 ATAGACTTGT ATCTTTGAGC CCGAACTCAC TCTTCTCGAA CGTGTCCGTT GCTCTGTGTA

1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650
 * * * * *
 TGCCCTCTCG AGCTGGGAGA CAAAGGAGGA ATTTACTTTC TTCACCAAGT GCAATAGATT
 ACGGAAGACC TCGACCCTCT GTTTCCTCCT TAAATGAAAG AAGTGGTTCA CGTTATCTAA

FIG. 6C

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1655 1660	1665 1670	1675 1680	1685 1690	1695 1700	1705 1710
ACTGATGTGA	TATTCTGTTG	CTTTACAGTT	ACAGTTGATG	TTTGGGGATC	GATGTGCTCA
TGACTACACT	ATAAGACAAC	GAAATGTCAA	TGTCAACTAC	AAACCCCTAG	CTACACGAGT
1715 1720	1725 1730	1735 1740	1745 1750	1755 1760	1765 1770
GCCAAATTTT	CTGTTTGAAA	TATCATGTTA	AATTAGAATG	AATTTATCTT	TACCAAAAAC
CGGTTTAAAG	GACAAACTTT	ATAGTACAAT	TTAATCTTAC	TTAAATAGAA	ATGGTTTTTG
1775 1780	1785 1790	1795 1800	1805 1810	1815 1820	1825 1830
CATGTTGCGT	TCAAAGAGGT	GAACATTAAA	ATATAGAGAC	AGGACAGAAT	GTGTTCTTTT
GTACAACGCA	AGTTTCTCCA	CTTGTAATTT	TATATCTCTG	TCCTGTCTTA	CACAAGAAAA
1835 1840	1845 1850	1855 1860	1865 1870	1875 1880	1885 1890
CTCCTCTACC	AGTCCTATTT	TTCAATGGGA	AGACTCAGGA	GTCTGCCACT	TGTCAAAGAA
GAGGAGATGG	TCAGGATAAA	AAGTTACCCT	TCTGAGTCCT	CAGACGGTGA	ACAGTTTCTT
1895 1900	1905 1910	1915 1920	1925 1930	1935 1940	1945 1950
GGTGCTGATC	CTAAGAATTT	TTCAATCTCA	GAATTCGGTG	TGCTGCCAAC	TTGATGTTCC
CCACGACTAG	GATTCTTAAA	AAGTAAGAGT	CTTAAGCCAC	ACGACGGTTG	AACTACAAGG
1955 1960	1965 1970	1975 1980	1985 1990	1995 2000	2005 2010
ACCTGCCACA	AACCACCAGG	ACTGAAAGAA	GAAAACAGTA	CAGAAGGCAA	AGTTTACAGA
TGGACGGTGT	TTGGTGGTCC	TGACTTTCTT	CTTTTGTGAT	GTCTTCCGTT	TCAAATGTCT
2015 2020	2025 2030	2035 2040	2045 2050	2055 2060	2065 2070
TGTTTTTAAT	TCTAGTATTT	TATCTGGAAC	AACCTGTAGC	AGCTATATAT	TTCCCCCTTG
ACAAAAATTA	AGATCATAAA	ATAGACCTTG	TTGAACATCG	TGGATATATA	AAGGGGAACC
2075 2080	2085 2090	2095 2100	2105 2110	2115 2120	2125 2130
TCCCAAGCCT	GATACTTTAG	CCATCATAAC	TCACTAACAG	GGAGAAGTAG	CTAGTAGCAA
AGGGTTCGGA	CTATGAAATC	GGTAGTATTG	AGTGATTGTC	CCTCTTCATC	GATCATCGTT
2135 2140	2145 2150	2155 2160	2165 2170	2175 2180	2185 2190
TGTGCCTTGA	TTGATTAGAT	AAAGATTTCT	AGTAGGCAGC	AAAAGACCAA	ATCTCAGTTG
ACACGGAACT	AACTAATCTA	TTTCTAAAGA	TCATCCGTCG	TTTTCTGGTT	TAGAGTCAAC
2195 2200	2205 2210	2215 2220	2225 2230	2235 2240	2245 2250
TTTGCTTCTT	GCCATCACTG	GTCCAGGTCT	TCAGTTTCCG	AATCTCTTTC	CCTTCCCCTG
AAACGAAGAA	CGGTAGTGAC	CAGGTCCAGA	AGTCAAAGGC	TTAGAGAAAG	GGAAGGGGAC
2255 2260	2265 2270	2275 2280	2285 2290	2295 2300	2305 2310
TGGTCTATTG	TCGCTATGTG	ACTTGCCTTT	AATCCAATAT	TTTGCTTTTT	TTCTATATCA
ACCAGATAAC	AGCGATACAC	TGAACGCGAA	TTAGGTTATA	AAACGGAAAA	AAGATATAGT
2315 2320	2325 2330	2335 2340	2345 2350	2355 2360	2365 2370
AAAAACCTTT	ACAGTTAGCA	GGGATGTTCC	TTACCGAGGA	TTTTTAACCC	CCAATCTCTC
TTTTTGAAAA	TGTCAATCGT	CCCTACAAGG	AATGGCTCCT	AAAAATTGGG	GGTTAGAGAG
2375 2380	2385 2390	2395 2400	2405 2410	2415 2420	2425 2430

FIG. 6D

SUBSTITUTE SHEET (RULE 26)

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ATAATCGCTA	GTGTTTAAAA	GGCTAAGAAT	AGTGGGGCCC	AACCGATGTG	GTAGGTGATA
TATTAGCGAT	CACAAATTTT	CCGATTCTTA	TCACCCCGGG	TTGGGTACAC	CATCCACTAT
2435 2440	2445 2450	2455 2460	2465 2470	2475 2480	2485 2490
AAGAGGCATC	TTTTCTAGAG	ACACATTGGA	CCAGATGAGG	ATCCGAAACG	GCAGCCTTTA
TTCTCCGTAG	AAAAGATCTC	TGTGTAACCT	GGTCTACTCC	TAGGCTTTTC	CCTCGGAAAT
2495 2500	2505 2510	2515 2520	2525 2530	2535 2540	2545 2550
CGTTCATCAC	CTGCTAGAAC	CTCTCGTAGT	CCATCACCAT	TTCTTGGCAT	TGGAATTCTA
GCAAGTAGTG	GACGATCTTC	GAGAGCATCA	GGTAGTGCTA	AAGAACCCTA	ACCTTAAGAT
2555 2560	2565 2570	2575 2580	2585 2590	2595 2600	2605 2610
CTGGAAAAAA	ATACAAAAAG	CAAAACAAAA	CCCTCAGCAC	TGTTACAAGA	GGCCATTTAA
GACCTTTTTT	TATGTTTTTC	CTTTTGTTC	GGGAGTCGTG	ACAATGTTCT	CCGGTAAATT
2615 2620	2625 2630	2635 2640	2645 2650	2655 2660	2665 2670
GTATCTTGTG	CTTCTTCACT	TACCCATTAG	CCAGGTTCTC	ATTAGGTTTT	GCTTGGGCCT
CATAGAACAC	GAAGAAGTCA	ATGGGTAATC	GGTCCAAGAG	TAATCCAAAA	CGAACCCGGA
2675 2680	2685 2690	2695 2700	2705 2710	2715 2720	2725 2730
CCCTGGCACT	GAACCTTAGG	CTTTGTATGA	CAGTGAAGCA	GCACTGTGAG	TGGTTCAAGC
GGGACCGTGA	CTTGGAATCC	GAAACATACT	GTCACTTCGT	CGTGACACTC	ACCAAGTTCC
2735 2740	2745 2750	2755 2760	2765 2770	2775 2780	2785 2790
ACACTGGAAT	ATAAAACAGT	CATGGCCTGA	GATGCAGGTG	ATGCCATTAC	AGAACCAAAT
TGTGACCTTA	TATTTTGTCA	GTACCGGACT	CTACGTCCAC	TACGGTAATG	TCTTGGTTTA
2795 2800	2805 2810	2815 2820	2825 2830	2835 2840	2845 2850
CGTGGCACGT	ATTGCTGTGT	CTCCTCTCAG	AGTGACAGTC	ATAAATACTG	TCAAACAATA
GCACCGTGCA	TAACGACACA	GAGGAGAGTC	TCACTGTCAG	TATTTATGAC	AGTTTGTAT
2855 2860	2865 2870	2875 2880	2885 2890	2895 2900	2905 2910
AAGGGAGAAT	GGTGCTGTTT	AAAGTCACAT	CCCTGTAAAT	TGCAGAATTC	AAAAGTGATT
TTCCCTCTTA	CCACGACAAA	TTTCAGTGTA	GGGACATTTA	ACGTCTTAAG	TTTTCACTAA
2915 2920	2925 2930	2935 2940	2945 2950	2955 2960	2965 2970
ATCTCTTTGA	TCTACTTGCC	TCATTTCCCT	ATCTTCTCCC	CCACGGTATC	CTAAACTTTA
TAGAGAAACT	AGATGAACGG	AGTAAAGGGA	TAGAAGAGGG	GGTGCCATAG	GATTTGAAAT
2975 2980	2985 2990	2995 3000	3005 3010	3015 3020	3025 3030
GACTTCCCAC	TGTTCTGAAA	GGAGACATTG	CTCTATGTCT	GCCTTCGACC	ACAGCAAGCC
CTGAAGGGTG	ACAAGACTTT	CCTCTGTAA	GAGATACAGA	CGGAAGCTGG	TGTCGTTCGG
3035 3040	3045 3050	3055 3060	3065 3070	3075 3080	3085 3090
ATCATCCTCC	ATTGCTCCCG	GGGACTCAAG	AGGAATCTGT	TTCTCTGCTG	TCAACTTCCC
TAGTAGGAGG	TAACGAGGGC	CCCTGAGTTC	TCCTTAGACA	AAGAGACGAC	AGTTGAAGGG
3095 3100	3105 3110	3115 3120	3125 3130	3135 3140	3145 3150
ATCTGGCTCA	GCAATAGGGT	ACTTTGCCAT	TATGCAAATG	GAGATAAAAG	CAATTCTGGC
TAGACCGAGT	CGTATCCAG	TGAAACGGTA	ATACGTTTAC	CTCTATTTTC	GTTAAGACCG

FIG. 6E

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3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210
*      *      *      *      *      *      *      *
TGTCCAGGAG CTAATCTGAC CGTTCTATTG TGTGGATGAC CACATAAGAA GGCAATTTTA
ACAGGTCCTC GATTAGACTG GCAAGATAAC ACACCTACTG GTGTATTCTT CCGTTAAAAT

3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270
*      *      *      *      *      *      *      *
GTGTATTAAT CATAGATTAT TATAAACTAT AAACCTTAAGG GCAAGGAGTT TATTACAATG
CACATAATTA GTATCTAATA ATATTTGATA TTTGAATTCC CGTTCCTCAA ATAATGTTAC

3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330
*      *      *      *      *      *      *      *
TATCTTTATT AAAACAAAAG GGTGTATAGT GTTCACAAAC TGTGAAAATA GTGTAAGAAC
ATAGAAATAA TTTTGTTTTC CCACATATCA CAAGTGTTTG ACACTTTTAT CACATTCTTG

3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390
*      *      *      *      *      *      *      *
TGTACATTGT GAGCTCTGCT TATTTTTCTC TTGTACCATA GAAAAATGTA TAAAAATTAT
ACATGTAACA CTCGAGACCA ATAAAAAGAG AACATGGTAT CTTTTTACAT ATTTTTAATA

3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450
*      *      *      *      *      *      *      *
CAAAAAGCTA ATGTGCAGGG ATATTGCCCTT ATTTGTCTGT AAAAAATGGA GCTCAGTAAC
GTTTTTCGAT TACACGTCCC TATAACGGAA TAAACAGACA TTTTTTACCT CGAGTCATTG

3455 3460 3465 3470 3475 3480 3485 3490 3495
*      *      *      *      *      *      *
ATAACTGCTT CTTGGAGCTT TGGAAATATTT TATCCTGTAT TCTTGTTT (SEQ ID NO:5)
TATTGACGAA GAACCTCGAA ACCTTATAAA ATAGGACATA AGAACAAA

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FIG. 6F

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      5      10      15      20      25      30      35      40      45      50
      *      *      *      *      *      *      *      *      *      *
CAACA ATG GCG GCT CCG AGC CCG AGC GGT GGC GGC GGC AGC GGC ACC CCC
GTTGT TAC CGC CGA GGC TCG GGC TCG CCA CCG CCG CCG TCG CCG TGG GGG
Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Thr Pro>

      55      60      65      70      75      80      85      90      95
      *      *      *      *      *      *      *      *      *
GGC CCC GTA GGG TCC CCG GCG CCA GGC CAC CCG GCC GTC AGC AGC ATG
CCG GGC CAT CCC AGG GGC CCG GGT CCG GTG GGC CCG CAG TCG TCG TAC
Gly Pro Val Gly Ser Pro Ala Pro Gly His Pro Ala Val Ser Ser Met>

100      105      110      115      120      125      130      135      140      145
      *      *      *      *      *      *      *      *      *      *
CAG GGT AAA CGC AAA GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC
GTC CCA TTT CCG TTT CGT GAC TTC AAC TTA AAA CGT TTA GGT GGA AAG
Gln Gly Lys Arg Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe>

      150      155      160      165      170      175      180      185      190
      *      *      *      *      *      *      *      *      *
AAA TCT ACA GCA AGG TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA
TTT AGA TGT CGT TCC AAA TGA GAC TTA GGG TTA GGA TGT CCT CAA GTT
Lys Ser Thr Ala Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln>

195      200      205      210      215      220      225      230      235      240
      *      *      *      *      *      *      *      *      *      *
AAC CCA CAC ATA GAG AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA
TTG GGT GTG TAT CTC TCT GAC TCT TGT GTG TCG TAA CTC AGT AGT CCT
Asn Pro His Ile Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly>

245      250      255      260      265      270      275      280      285      290
      *      *      *      *      *      *      *      *      *      *
AAA CTG AAG ATC TCC CCT GAA CAA CAC TGG GAT TTC ACT CCA GAG GAC
TTT GAC TTC TAG AGG GGA CTT GTT GTG ACC CTA AAG TGA CGT CTC CTG
Lys Leu Lys Ile Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp>

295      300      305      310      315      320      325      330      335
      *      *      *      *      *      *      *      *      *
TTG AAA GAC CTT GGA GAA ATT GGA CGA GGA GCT TAT GGT TCT GTC AAC
AAC TTT CTG GAA CCT CTT TAA CCT GCT CCT CGA ATA CCA AGA CAG TTG
Leu Lys Asp Leu Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn>

340      345      350      355      360      365      370      375      380      385
      *      *      *      *      *      *      *      *      *      *
AAA ATG GTC CAC AAA CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT
TTT TAC CAG GTG TTT GGT TCA CCC GTT TAT TAC CGT CAA TTT TCT TAA
Lys Met Val His Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile>

390      395      400      405      410      415      420      425      430
      *      *      *      *      *      *      *      *      *
CGG TCA ACA GTG GAT GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG
GCC AGT TGT CAC CTA CTT TTT CTT GTT TTT GTT GAA GAA TAC CTA AAC
Arg Ser Thr Val Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu>

435      440      445      450      455      460      465      470      475      480
      *      *      *      *      *      *      *      *      *      *
GAT GTA GTA ATG CGG AGT AGT GAT TGC CCA TAC ATT GTT CAG TTT TAT
CTA CAT CAT TAC GCC TCA TCA CTA ACG GGT ATG TAA CAA GTC AAA ATA
Asp Val Val Met Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr>

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FIG. 7A

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485 490 495 500 505 510 515 520 525 530
 * * * * * * * * *
 GGT GCA CTC TTC AGA GAG GGT GAC TGT TGG ATC TGT ATG GAA CTC ATG
 CCA CGT GAG AAG TCT CTC CCA CTG ACA ACC TAG ACA TAC CTT GAG TAC
 Gly Ala Leu Phe Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met>

 535 540 545 550 555 560 565 570 575
 * * * * * * * * *
 TCT ACC TCG TTT GAT AAG TTT TAC AAA TAT GTA TAT AGT GTA TTA GAT
 AGA TGG AGC AAA CTA TTC AAA ATG TTT ATA CMT ATA TCA CAT AAT CTA
 Ser Thr Ser Phe Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp>

 580 585 590 595 600 605 610 615 620 625
 * * * * * * * * *
 GAT GTT ATT CCA GAA GAA ATT TTA GGC AAA ATC ACT TTA GCA ACT GTG
 CTA CAA TAA GGT CTT CTT TAA AAT CCG TTT TAG TGA AAT CGT TGA CAC
 Asp Val Ile Pro Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val>

 630 635 640 645 650 655 660 665 670
 * * * * * * * * *
 AAA GCA CTA AAC CAC TTA AAA GAA AAC TTG AAA ATT ATT CAC AGA GAT
 TTT CGT GAT TTG GTG AAT TTT CTT TTG AAC TTT TAA TAA GTG TCT CTA
 Lys Ala Leu Asn His Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp>

 675 680 685 690 695 700 705 710 715 720
 * * * * * * * * *
 ATC AAA CCT TCC AAT ATT CTT CTG GAC AGA AGT GGA AAT ATT AAG CTC
 TAG TTT GGA AGG TTA TAA GAA GAC CTG TCT TCA CCT TTA TAA TTC GAG
 Ile Lys Pro Ser Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu>

 725 730 735 740 745 750 755 760 765 770
 * * * * * * * * *
 TGT GAC TTC GGC ATC AGT GGA CAG CTT GTG GAC TCT ATT GCC AAG ACA
 ACA CTG AAG CCG TAG TCA CCT GTC GAA CAC CTG AGA TAA CCG TTC TGT
 Cys Asp Phe Gly Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr>

 775 780 785 790 795 800 805 810 815
 * * * * * * * * *
 AGA GAT GCT GGC TGT AGG CCA TAC ATG GCA CCT GAA AGA ATA GAC CCA
 TCT CTA CGA CCG ACA TCC GGT ATG TAC CGT GGA CTT TCT TAT CTG GGT
 Arg Asp Ala Gly Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro>

 820 825 830 835 840 845 850 855 860 865
 * * * * * * * * *
 AGC GCA TCA CGA CAA GGA TAT GAT GTC CGC TCT GAT GTC TGG AGT TTG
 TCG CGT AGT GCT GTT CCT ATA CTA CAG GCG AGA CTA CAG ACC TCA AAC
 Ser Ala Ser Arg Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu>

 870 875 880 885 890 895 900 905 910
 * * * * * * * * *
 GGG ATC ACA TTG TAT GAG TTG GCC ACA GGC CGA TTT CCT TAT CCA AAG
 CCC TAG TGT AAC ATA CTC AAC CCG TGT CCG GCT AAA GGA ATA GGT TTC
 Gly Ile Thr Leu Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys>

 915 920 925 930 935 940 945 950 955 960
 * * * * * * * * *
 TGG AAT AGT GTA TTT GAT CAA CTA ACA CAA GTC GTG AAA GGA GAT CCT
 ACC TTA TCA CAT AAA CTA GTT GAT TGT GTT CAG CAC TTT CCT CTA GGA
 Trp Asn Ser Val Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro>

 965 970 975 980 985 990 995 1000 1005 1010
 * * * * * * * * *

FIG. 7B

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CCG CAG CTG AGT AAT TCT GAG GAA AGG GAA TTC TCC CCG AGT TTC ATC
GGC GTC GAC TCA TTA AGA CTC CTT TCC CTT AAG AGG GGC TCA AAG TAG
Pro Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile>

1015 1020 1025 1030 1035 1040 1045 1050 1055
AAC TTT GTC AAC TTG TGC CTT ACG AAG GAT GAA TCC AAA AGG CCA AAG
TTG AAA CAG TTG AAC ACG GAA TGC TTC CTA CTT AGG TTT TCC GGT TTC
Asn Phe Val Asn Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys>

1060 1065 1070 1075 1080 1085 1090 1095 1100 1105
TAT AAA GAG CTT CTG AAA CAT CCC TTT ATT TTG ATG TAT GAA GAA CGT
ATA TTT CTC GAA GAC TTT GTA GGG AAA TAA AAC TAC ATA CTT CTT GCA
Tyr Lys Glu Leu Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg>

1110 1115 1120 1125 1130 1135 1140 1145 1150
GCC GTT GAG GTC GCA TGC TAT GTT TGT AAA ATC CTG GAT CAA ATG CCA
CGG CAA CTC CAG CGT ACG ATA CAA ACA TTT TAG GAC CTA GTT TAC GGT
Ala Val Glu Val Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro>

1155 1160 1165 1170 1175 1180 1185 1190 1195 1200
GCT ACT CCC AGC TCT CCC ATG TAT GTC GAT TGATAT CGYTGCTACA
CGA TGA GGG TCG AGA GGG TAC ATA CAG CTA ACTATA GCRACGATGT
Ala Thr Pro Ser Ser Pro Met Tyr Val Asp> (SEQ ID NO:8)

1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260
TCAGACTCTA GAAAAAAGGG CTGAGAGGAA GCAAGACGTA AAGAATTTTC ATCCCGTATC
AGTCTGAGAT CTTTTTCCCG GACTCTCCTT CGTCTGTCAT TTCTTAAAAG TAGGGCATAG

1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320
ACAGTGTTTT TATTGCTCCG CCAGACACCA TGTGCAATAA GATTGGTGTT CGTTTCCATC
TGTCACAAAA ATAACGAGCG GGTCTGTGGT ACACGTTATT CTAACCACAA GCAAAGGTAG

1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380
ATGTCTGTAT ACTCCTGTCA CCTAGAACGT GCATCCTTGT AATACCTGAT TGATCACACA
TACAGACATA TGAGGACAGT GGATCTTGCA CGTAGGAACA TTATGGACTA ACTAGTGTGT

1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440
GTGTTAGTGC TGGTCAGAGA GACCTCATCC TGCTCTTTTG TGATGAACAT ATTCATGAAA
CACAATCAGC ACCAGTCTCT CTGGAGTAGG ACGAGAAAAC ACTACTTGTA TAAGTACTTT

1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500
TGTGGAAGTC AGTACGATCA AGTGTGTTGAC TGTGATTAGA TCACATCTTA AATTCATTTT
ACACCTTCAG TCATGCTAGT TCAACAACCTG ACACTAATCT AGTGTAGAAT TTAAGTAAAG

1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560
TAGACTCAAA ACCTGGAGAT GCAGCTACTG GAATGGTGTT TTGTCAGACT TCCAAATCCT
ATCTGAGTTT TGGACCTCTA CGTCGATGAC CTTACCACAA AACAGTCTGA AGGTTTAGGA

1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620
GGAAGGACAC AGTGATGAAT GTACTATATC TGAACATAGA AACTCGGGCT TGAGTGAGAA
CCTTCCTGTG TCACTACTTA CATGATATAG ACTGTATCT TTAGAGCCCGA ACTCACTCTT

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FIG. 7C

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1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680
GAGCTTGCAC AGCCAACGAG ACACATTGCC TTCTGGAGCT GGGAGACAAA GGAGGAATTT
CTCGAACGTG TCGGTTCGTC TGTGTAACGG AAGACCTCGA CCCTCTGTTT CCTCCTTAAA

1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740
ACTTTCCTCA CCAAGTGCAA TAGATTACTG ATGTGATATT CTGTTGCTTT ACAGTTACAG
TGAAAGAAGT GGTTCACGTT ATCTAATGAC TACACTATAA GACAACGAAA TGTCAATGTC

1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800
TTGATGTTTG GGGATCGATG TGCTCAGCCA AATTCCTGTG TTGAAATATC ATGTTAAATT
AACTACAAAC CCTTAGCTAC ACGAGTCGGT TTAAAGGACA AACTTTATAG TACAATTTAA

1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860
AGAATGAATT TATCTTTACC AAAAACCATG TTGCGTTCAA AGAGGTGAAC ATTAAAATAT
TCTTACTTAA ATAGAAATGG TTTTGGTAC AACGCAAGTT TCTCCACTTC TAATTTTATA

1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920
AGAGACAGGA CAGAATGTGT TCTTTTCTCC TCTACCAGTC CTATTTTCA ATGGAAGAC
TCTCTGTCTT GTCTTACACA AGAAAAGAGG AGATGGTCAG GATAAAAAGT TACCCTTCTG

1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980
TCAGGAGTCT GCCACTTGTG AAAGAAGGTG CTGATCCTAA GAATTTTCA TTCTCAGAAT
AGTCTTCAGA CCGTGAACAG TTTCTTCCAC GACTAGGATT CTTAAAAAGT AAGAGTCTTA

1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040
TCGGTGTGCT GCCAACTTGA TGTTCACCTT GCCACAAACC ACCAGGACTG AAAGAAGAAA
AGCCACACGA CCGTTGAACT ACAAGGTGGA CCGTGTGTTG TGGTCCTGAC TTTCTTCTTT

2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100
ACAGTACAGA AGGCAAAGTT TACAGATGTT TTTAATTCTA GTATTTTATC TGAACAACCT
TGTATGTCTT TCCGTTTCAA ATGTCTACAA AAATTAAGAT CATAAAATAG ACCTTGTGTA

2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160
TGTAGCAGCT ATATATTTCC CCTTGGTCCC AAGCCTGATA CTTTAGCCAT CATAACTCAC
ACATCGTCTG TATATAAAGG GGAACCAGGG TTCGGACTAT GAAATCGGTA GTATTGAGTG

2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220
TAACAGGGAG AAGTAGCTAG TAGCAATGTG CTTTGATTGA TTAGATAAAG ATTTCTAGTA
ATTGTCCCTC TTCATCGATC ATCGTTACAC GGAACCTAAT AATCTATTTT TAAAGATCAT

2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280
GGCAGCAAAA GACCAAATCT CAGTTGTTTG CTTCTTGCCA TCACTGGTCC AGGTCTTCAG
CCGTCGTTTT CTGGTTTAGA GTCAACAAAC GAAGAACGGT AGTGACCAGG TCCAGAAGTC

2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340
TTTCCGAATC TCTTTCCCTT CCCCTGTGGT CTATTGTGCG TATGTGACTT GCGCTTAATC
AAAGGCTTAG AGAAAGGGAA GGGGACACCA GATAACAGCG ATACACTGAA CGCGAATTAG

2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400

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FIG. 7D

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CAATATTTTG CTTTTTTCT ATATCAAAAA ACCTTTACAG TTAGCAGGGA TGTTCCTTAC
GTTATAAAAC GGAAAAAAGA TATAGTTTTT TGGAAATGTC AATCGTCCCT ACAAGGAATG

2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460
CGAGGATTTT TAACCCCCAA TCTCTCATAA TCGCTAGTGT TTAAAAGGCT AAGAATAGTG
GCTCCTAAAA ATTGGGGGTT AGAGAGTATT AGCGATCACA AATTTTCCGA TTCTTATCAC

2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520
GGGCCCAACC GATGTGGTAG GTGATAAAGA GGCATCTTTT CTAGAGACAC ATTGGACCAG
CCCGGGTTGG CTACACCATC CACTATTCTT CCGTAGAAAA GATCTCTGTG TAACCTGGTC

2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580
ATGAGGATCC GAAACGGCAG CTTTTACGTT CATCACCTGC TAGAACCTCT CGTAGTCCAT
TACTCCTAGG CTTTGCCGTC GGAAATGCAA GTAGTGGACG ATCTTGGAGA GCATCAGGTA

2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640
CACCATTTCT TGGCATTGGA ATTCTACTGG AAAAAAATAC AAAAAGCAAA ACAAAACCCT
GTGGTAAAGA ACCGTAACCT TAAGATGACC TTTTTTTATG TTTTTCGTTT TGTTTTGGGA

2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700
CAGCACTGTT ACAAGAGGCC ATTTAAGTAT CTGTGCTTTC TTCACTTACC CATTAGCCAG
GTCTGTACAA TGTTCTCCGG TAAATTCATA GAACACGAAG AAGTGAATGG GTAATCGGTC

2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760
GTTCTCATTA GGTTTTGCTT GGGCCTCCCT GGCCTGAAC CTTAGGCTTT STATGACAGT
CAAGAGTAAT CCAAAACGAA CCCGGAGGGA CCGTGACTTG GAATCCGAAA CATACTGTCA

2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820
GAAGCAGCAC TGTGAGTGGT TCAAGCACAC TGAATATAA AACAGTCATG GCCTGAGATG
CTTCGTCGTG AACTCACCAC AGTTCGTGTG ACCTTATATT TTGTCAGTAC CGGACTCTAC

2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880
CAGGTGATGC CATTACAGAA CCAAATCGTG GCACGTATTG CTGTGCTCTC TCTCAGAGTG
GTCCACTACG GTAATGTCCT GGTTTAGCAC CGTGCCATAAC GACACAGAGG AGAGTCTCAC

2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940
ACAGTCATAA ATACTGTCAA ACAATAAAGG GAGAATGGTG CTGTTTAAAG TCACATCCCT
TGTCAGTATT TATGACAGTT TGTTATTTC CTTTACCAC GACAAATTTT AGTGTAGGGA

2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000
GTAAATTGCA GAATTCAAAA GTGATTATCT CTTTGATCTA CTTGCCTCAT TTCCCTATCT
CATTTAACGT CTTAAGTTTT CACTAATAGA GAAACTAGAT GAACGGAGTA AAGGGATAGA

3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060
TCTCCCCCAC GGTATCCTAA ACTTTAGACT TCCCCTGTT CTGAAAGGAG ACATTGCTCT
AGAGGGGGTG CCATAGGATT TGAAATCTGA AGGGTGACAA GACTTTCCTC TGTAACGAGA

3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120
ATGTCTGCCT TCGACCACAG CAAGCCATCA TCCTCCATTG CTCCCGGGGA CTCAAGAGGA

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FIG. 7E

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TACAGACGGA AGCTGGTGTC GTTCGGTAGT AGGAGGTAAC GAGGGCCCCCT GAGTTCTCCT
3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180
* * * * *
ATCTGTTTTCT CTGCTGTCAA CTTCCCATCT GGCCTCAGCAT AGGGTCACCTT TCCCATTTATG
TAGACAAAGA GACGACAGTT GAAGGGTAGA CCGAGTCGTA TCCCAGTGAA ACGGTAATAC
3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240
* * * * *
CAAATGGAGA TAAAAGCAAT TCTGGCTGTC CAGGAGCTAA TCTGACCGTT CTATTGTGTG
GTTTACCTCT ATTTTCGTTA AGACCGACAG GTCCTCGATT AGACTGGCAA GATAACACAC
3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300
* * * * *
GATGACCACA TAAGAAGGCA ATTTTAGTGT APTAATCATA GATTATTATA AACTATAAAC
CTACTGGTGT ATTCTTCCGT TAAAATCACA TAATTAGTAT CTAATAATAT TTGATATTTG
3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360
* * * * *
TTAAGGGCAA GGAGTTTATT ACAATGTATC TTTATTAAAA CAAAAGGGTG TATAGTGTTC
AATTCCCGTT CCTCAAATAA TGTTACATAG AAATAATTTT GTTTTCCAC ATATCACAAG
3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420
* * * * *
ACAAACTGTG AAAATAGTGT AAGAACTGTA CATTGTGAGC TCTGGTTATT TTTCTCTTGT
TGTTTGACAC TTTTATCACA TTCTTGACAT GTAACACTCG AGACCAATAA AAAGAGAACA
3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480
* * * * *
ACCATAGAAA AATGTATAAA AATTATCAAA AAGCTAATGT GCAGGGATAT TGCCTTATTT
TGGTATCTTT TTACATATTT TTAATAGTTT TTCGATTACA CGTCCCTATA ACGGAATAAA
3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540
* * * * *
GTCTGTAAAA AATGGAGCTC AGTAACATAA CTGCTTCTTG GAGCTTTGGA ATATTTTATC
CAGACATTTT TTACCTCGAG TCATTGTATT GACGAAGAAC CTCGAAACCT TATAAAATAG
3545 3550
*
CTGTATTCTT GTTT (SEQ ID NO:7)
GACATAAGAA CAAA

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FIG. 7F

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      5      10      15      20      25      30      35      40      45      50
      *      *      *      *      *      *      *      *      *      *
CTCCCAACA ATG GCG GCT CCG AGC CCG AGC GGC GGC GGC GGC TCC GGG GGC
GAGGGTTGT TAC CGC CGA GGC TCG GGC TCG CCG CCG CCG CCG AGG CCC CCG
      Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Gly>

      55      60      65      70      75      80      85      90      95
      *      *      *      *      *      *      *      *      *
GGC AGC GGC AGC GGC ACC CCC GGC CCC GTA GGC TCC CCG GCG CCA GGC
CCG TCG CCG TCG CCG TCG GGC CCG GGC CAT CCC AGG GGC CCG GGT CCG
Gly Ser Gly Ser Gly Thr Pro Gly Pro Val Gly Ser Pro Ala Pro Gly>

100      105      110      115      120      125      130      135      140      145
      *      *      *      *      *      *      *      *      *      *
CAC CCG GCC GTC AGC AGC ATG CAG GGT AAA CGC AAA GCA CTG AAG TTG
GTG GGC CCG CAG TCG TCG TCG GTC CCA TTT GCG TTT CGT GAC TTC AAC
His Pro Ala Val Ser Ser Met Gln Gly Lys Arg Lys Ala Leu Lys Leu>

      150      155      160      165      170      175      180      185      190      195
      *      *      *      *      *      *      *      *      *      *
AAT TTT GCA AAT CCA CCT TTC AAA TCT ACA GCA AGG TTT ACT CTG AAT
TTA AAA CGT TTA GGT GGA AAG TTT AGA TGT CGT TCC AAA TGA GAC TTA
Asn Phe Ala Asn Pro Pro Phe Lys Ser Thr Ala Arg Phe Thr Leu Asn>

      200      205      210      215      220      225      230      235      240
      *      *      *      *      *      *      *      *      *
CCC AAT CCT ACA GGA GTT CAA AAC CCA CAC ATA GAG AGA CTG AGA ACA
GGG TTA GGA TGT CCT CAA GTT TTG GGT GTG TAT CTC TCT GAC TCT TGT
Pro Asn Pro Thr Gly Val Gln Asn Pro His Ile Glu Arg Leu Arg Thr>

245      250      255      260      265      270      275      280      285      290
      *      *      *      *      *      *      *      *      *      *
CAC AGC ATT GAG TCA TCA GGA AAA CTG AAG ATC TCC CCT GAA CAA CAC
GTG TCG TAA CTC AGT AGT CCT TTT GAC TTC TAG AGG GGA CTT GTT GTG
His Ser Ile Glu Ser Ser Gly Lys Leu Lys Ile Ser Pro Glu Gln His>

      295      300      305      310      315      320      325      330      335
      *      *      *      *      *      *      *      *      *
TGG GAT TTC ACT GCA GAG GAC TTG AAA GAC CTT GGA GAA ATT GGA CGA
ACC CTA AAG TGA CGT CTC CTG AAC TTT CTG GAA CCT CTT TAA COT GCT
Trp Asp Phe Thr Ala Glu Asp Leu Lys Asp Leu Gly Glu Ile Gly Arg>

340      345      350      355      360      365      370      375      380      385
      *      *      *      *      *      *      *      *      *      *
GGA GCT TAT GGT TCT GTC AAC AAA ATG GTC CAC AAA CCA AGT GGG CAA
CCT CGA ATA CCA AGA CAG TTG TTT TAC CAG GTG TTT GGT TCA CCC GTT
Gly Ala Tyr Gly Ser Val Asn Lys Met Val His Lys Pro Ser Gly Gln>

      390      395      400      405      410      415      420      425      430      435
      *      *      *      *      *      *      *      *      *      *
ATA ATG GCA GTT AAA AGA ATT CGG TCA ACA GTG GAT GAA AAA GAA CAA
TAT TAC CGT CAA TTT TCT TAA GCC AGT TGT CAC CTA CTT TTT CTT GTT
Ile Met Ala Val Lys Arg Ile Arg Ser Thr Val Asp Glu Lys Glu Gln>

      440      445      450      455      460      465      470      475      480
      *      *      *      *      *      *      *      *      *
AAA CAA CTT CTT ATG GAT TTG GAT GTA GTA ATG CGG AGT AGT GAT TGC
TTT GTT GAA GAA TAC CTA AAC CTA CAT CAT TAC GCC TCA TCA CTA ACG
Lys Gln Leu Leu Met Asp Leu Asp Val Val Met Arg Ser Ser Asp Cys>

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FIG. 8A

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485      490      495      500      505      510      515      520      525      530
      *      *      *      *      *      *      *      *      *
CCA TAC ATT GTT CAG TTT TAT GGT GCA CTC TTC AGA GAG GGT GAC TGT
GGT ATG TAA CAA GTC AAA ATA CCA CGT GAG AAG TCT CTC CCA CTG ACA
Pro Tyr Ile Val Gln Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Cys>

535      540      545      550      555      560      565      570      575
      *      *      *      *      *      *      *      *      *
TGG ATC TGT ATG GAA CTC ATG TCT ACC TCG TTT GAT AAG TTT TAC AAA
ACC TAG ACA TAC CTT GAG TAC AGA TGG AGC AAA CTA TTC AAA ATG TTT
Trp Ile Cys Met Glu Leu Met Ser Thr Ser Phe Asp Lys Phe Tyr Lys>

580      585      590      595      600      605      610      615      620      625
      *      *      *      *      *      *      *      *      *
TAT GTA TAT AGT GTA TTA GAT GAT GTT ATT CCA GAA GAA ATT TTA GGC
ATA CAT ATA TCA CAT AAT CTA CTA CAA TAA GGT CTT CTT TAA AAT CCG
Tyr Val Tyr Ser Val Leu Asp Asp Val Ile Pro Glu Glu Ile Leu Gly>

630      635      640      645      650      655      660      665      670      675
      *      *      *      *      *      *      *      *      *
AAA ATC ACT TTA GCA ACT GTG AAA GCA CTA AAC CAC TTA AAA GAA AAC
TTT TAG TGA AAT CGT TGA CAC TTT CGT GAT TTG GTG AAT TTT CTT TTG
Lys Ile Thr Leu Ala Thr Val Lys Ala Leu Asn His Leu Lys Glu Asn>

680      685      690      695      700      705      710      715      720
      *      *      *      *      *      *      *      *      *
TTG AAA ATT ATT CAC AGA GAT ATC AAA CCT TCC AAT ATT CTT CTG GAC
AAC TTT TAA TAA GTG TCT CTA TAG TTT GGA AGG TTA TAA GAA GAC CTG
Leu Lys Ile Ile His Arg Asp Ile Lys Pro Ser Asn Ile Leu Leu Asp>

725      730      735      740      745      750      755      760      765      770
      *      *      *      *      *      *      *      *      *
AGA AGT GGA AAT ATT AAG CTC TGT GAC TTC GGC ATC AGT GGA CAG CTT
TCT TCA CCT TTA TAA TTC GAG ACA CTG AAG CCG TAG TCA CCT GTC GAA
Arg Ser Gly Asn Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Gln Leu>

775      780      785      790      795      800      805      810      815
      *      *      *      *      *      *      *      *      *
GTG GAC TCT ATT GCC AAG ACA AGA GAT GGT GGC TGT AGG CCA TAC ATG
CAC CTG AGA TAA CGG TTC TGT TCT CTA CGA CCG ACA TCC GGT ATG TAC
Val Asp Ser Ile Ala Lys Thr Arg Asp Ala Gly Cys Arg Pro Tyr Met>

820      825      830      835      840      845      850      855      860      865
      *      *      *      *      *      *      *      *      *
GCA CCT GAA AGA ATA GAC CCA AGC GCA TCA CGA CAA GGA TAT GAT GTC
CGT GGA CTT TCT TAT CTG GGT TCG CGT AGT GCT GTT CCT ATA CTA CAG
Ala Pro Glu Arg Ile Asp Pro Ser Ala Ser Arg Gln Gly Tyr Asp Val>

870      875      880      885      890      895      900      905      910      915
      *      *      *      *      *      *      *      *      *
CGC TCT GAT GTC TGG AGT TTG GGG ATC ACA TTG TAT GAG TTG GCC ACA
GCG AGA CTA CAG ACC TCA AAC CCC TAG TGT AAC ATA CTC AAC CGG TGT
Arg Ser Asp Val Trp Ser Leu Gly Ile Thr Leu Tyr Glu Leu Ala Thr>

920      925      930      935      940      945      950      955      960
      *      *      *      *      *      *      *      *      *
GGC CGA TTT CTT TAT CCA AAG TGG AAT AGT GTA TTT GAT CAA CTA ACA
CCG GCT AAA GGA ATA GGT TTC ACC TTA TCA CAT AAA CTA GTT GAT TGT
Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val Phe Asp Gln Leu Thr>

965      970      975      980      985      990      995      1000      1005      1010
      *      *      *      *      *      *      *      *      *

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FIG. 8B

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CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT AAT TCT GAG GAA AGG
GTT CAG CAC TTT CCT CTA GGA GGC GTC GAC TCA TTA AGA CTC CTT TCC
Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser Asn Ser Glu Glu Arg>

1015 1020 1025 1030 1035 1040 1045 1050 1055
* * * * *
GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC TTG TGC CTT ACG AAG
CTT AAG AGG GGC TCA AAG TAG TTG AAA CAG TTG AAC ACG GAA TGC TTC
Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Asn Leu Cys Leu Thr Lys>

1060 1065 1070 1075 1080 1085 1090 1095 1100 1105
* * * * *
GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT CTG AAA CAT CCC TTT
CTA CTT AGG TTT TCC GGT TTC ATA TTT CTC GAA GAC TTT GTA GGG AAA
Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu Leu Lys His Pro Phe>

1110 1115 1120 1125 1130 1135 1140 1145 1150 1155
* * * * *
ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC GCA TGC TAT GTT TGT
TAA AAC TAC ATA CTT CTT GCA CGG CAA CTC CAG CGT ACG ATA CAA ACA
Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val Ala Cys Tyr Val Cys>

1160 1165 1170 1175 1180 1185 1190 1195 1200
* * * * *
AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC TCT CCC ATG TAT GTC
TTT TAG GAC CTA GTT TAC GGT CGA TGA GGG TCG AGA GGG TAC ATA CAG
Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser Ser Pro Met Tyr Val>

1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260
* * * * *
GAT TGAT ATCGCTGCTA CATCAGACTC TAGAAAAAAG GGCTGAGAGG AAGCAAGACG
CTA ACTA TAGCGACGAT GTAGTCTGAG ATCTTTTTTTC CCGACTCTCC TTCGTTCTGC
Asp> (SEQ ID NO:10)

1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320
* * * * *
TAAAGAATTT TCATCCCGTA TCACAGTGT TTTATTGCTC GCCCAGACAC CATGTGCAAT
ATTTCTTAAA AGTAGGGCAT AGTGTCACAA AAATAACGAG CGGGTCTGTG GTACACGTTA

1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380
* * * * *
AAGATTGGTG TTCGTTTCCA TCATGTCTGT ATACTCCTGT CACCTAGAAC GTGCATCCTT
TTCTAACCAC AAGCAAAGGT AGTACAGACA TATGAGGACA GTGGATCTTG CACGTAGGAA

1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440
* * * * *
GTAATACCTG ATTGATCACA CAGTGTTAGT GCTGGTCAGA GAGACCTCAT COTGCTCTTT
CATTATGGAC TAACTAGTGT GTCACAATCA CGACCAGTCT CTCTGGAGTA GGACGAGAAA

1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500
* * * * *
TGTGATGAAC ATATTCATGA AATGTGGAAG TCAGTACGAT CAAGTTGTTG ACTGTGATTA
ACACTACTTG TATAAGTACT TTACACCTTC AGTCATGCTA GTTCAACAAC TGACACTAAT

1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560
* * * * *
GATCACATCT TAAATTCATT TCTAGACTCA AAACCTGGAG ATGCAGCTAC TGAATGGTG
CTAGTGTAGA ATTTAAGTAA AGATCTGAGT TTTGGACCTC TACGTGGATG ACCTTACCAC

1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620
* * * * *
TTTTGTCAGA CTTCCAAATC CTGGAAGGAC ACAGTGATGA ATGTACTATA TCTGAACATA

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FIG. 8C

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AAAACAGTCT	GAAGGTTTAG	GACCTTCCTG	TGTCACTACT	TACATGATAT	AGACTTGTAT
1625 1630	1635 1640	1645 1650	1655 1660	1665 1670	1675 1680
GAAACTCGGG	CTTGAGTGAG	AAGAGCTTGC	ACAGCCAACG	AGACACATTG	CCTTCTGGAG
CTTTGAGCCC	GAACTCAGTC	TTCTCGAACG	TGTCGGTTGC	TCTGTGTAAC	GGAGACCTC
1685 1690	1695 1700	1705 1710	1715 1720	1725 1730	1735 1740
CTGGGAGACA	AAGGAGGAAT	TTACTTTCTT	CACCAAGTGC	AATAGATTAC	TGATGTGATA
GACCTCTGT	TTCTCTCTTA	AATGAAAGAA	GTGGTTCACG	TTATCTAATG	ACTACACTAT
1745 1750	1755 1760	1765 1770	1775 1780	1785 1790	1795 1800
TTCTGTTGCT	TTACAGTTAC	AGTTGATGTT	TGGGGATCGA	TGTGCTCAGC	CAAATTTCTT
AAGACAACGA	AATGTCAATG	TCAACTACAA	ACCCCTAGCT	ACACGAGTCG	GTTTAAAGGA
1805 1810	1815 1820	1825 1830	1835 1840	1845 1850	1855 1860
GTTTGAAATA	TCATGTTAAA	TTAGAATGAA	TTTATCTTTA	CCAAAAACCA	TGTTGCGTTC
CAAACTTTAT	AGTACAATTT	AATCTTACTT	AAATAGAAAT	GGTTTTTGGT	ACAACGCAAG
1865 1870	1875 1880	1885 1890	1895 1900	1905 1910	1915 1920
AAAGAGGTGA	ACATTAAAAAT	ATAGAGACAG	GACAGAATGT	GTTCTTTTCT	CCTCTACCAG
TTTCTCCACT	TGTAATTTTA	TATCTCTGTC	CTGTCTTACA	CAAGAAAAGA	GGAGATGGTC
1925 1930	1935 1940	1945 1950	1955 1960	1965 1970	1975 1980
TCCTATTTTT	CAATGGGAAG	ACTCAGGAGT	CTGCCACTTG	TCAAAGAAGG	TGCTGATCCT
AGGATAAAAA	GTTACCCCTC	TGAGTCCTCA	GACGGTGAAC	AGTTTCTTCC	ACGACTAGGA
1985 1990	1995 2000	2005 2010	2015 2020	2025 2030	2035 2040
AAGAATTTTT	CATTCTCAGA	ATTCCGGTGTG	CTGCCAACTT	GATGTTCCAC	CTGCCACAAA
TTCTTAAAAA	GTAAGAGTCT	TAAGCCACAC	GACGGTTGAA	CTACAAGGTG	GACGGTGTTC
2045 2050	2055 2060	2065 2070	2075 2080	2085 2090	2095 2100
CCACCAGGAC	TGAAAGAAGA	AAACAGTACA	GAAGGCAAAG	TTTACAGATG	TTTTTAATTC
GGTGGTCCIG	ACTTTCTTCT	TTTGTCATGT	CTTCCGTTTC	AAATGTCTAC	AAAAATTAAG
2105 2110	2115 2120	2125 2130	2135 2140	2145 2150	2155 2160
TAGTATTTTA	TCTGGAACAA	CTTGTAGCAG	CTATATATTT	CCCCTTGGTC	CCAAGCCTGA
ATCATAAAAT	AGACCTTGTT	GAACATCGTC	GATATATAAA	GGGGAACCAG	GGTTCGGACT
2165 2170	2175 2180	2185 2190	2195 2200	2205 2210	2215 2220
TACTTTAGCC	ATCATAACTC	ACTAACAGGG	AGAAGTAGCT	AGTAGCAATG	TGCCTTGATT
ATGAAATCGG	TAGTATTGAG	TGATTGTCCC	TCTTCATCGA	TCATCGTTAC	ACGGAACATA
2225 2230	2235 2240	2245 2250	2255 2260	2265 2270	2275 2280
GATTAGATAA	AGATTTCTAG	TAGGCAGCAA	AAGACCAAAT	CTCAGTTGTT	TGCTTCTTGC
CTAATCTATT	TCTAAAGATC	ATCCGTCGTT	TTCTGGTTTA	GAGTCAACAA	ACGAAGAACG
2285 2290	2295 2300	2305 2310	2315 2320	2325 2330	2335 2340
CATCACTGGT	CCAGGTCTTC	AGTTTCCGAA	TCTCTTTCCC	TTCCCTGTG	GTCTATTGTC
GTAGTGACCA	GGTCCAGAAG	TCAAAGGCTT	AGAGAAAGGG	AAGGGGACAC	CAGATAACAG

FIG. 8D

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2345	2350	2355	2360	2365	2370	2375	2380	2385	2390	2395	2400
GCTATGTGAC	TTGCGCTTAA	TCCAATATTT	TGCCTTTTTTT	CTATATCAAA	AAACCTTTAC						
CGATACACTG	AACGCGAATT	AGGTTATAAA	ACGGAAAAAA	GATATAGTTT	TTTGGAATG						
2405	2410	2415	2420	2425	2430	2435	2440	2445	2450	2455	2460
AGTTAGCAGG	GATGTTCCCT	ACCGAGGATT	TTTAACCCCC	AATCTCTCAT	AATCGCTAGT						
TCAATCGTCC	CTACAAGGAA	TGGCTCCCTA	AAATTGGGGG	TTAGAGAGTA	TTAGCGATCA						
2465	2470	2475	2480	2485	2490	2495	2500	2505	2510	2515	2520
GTTTAAAAGG	CTAAGAATAG	TGGGGCCCCA	CCSATGTGGT	AGGTGATAAA	GAGGCATCTT						
CAAAATTTTCC	GATTCTTATC	ACCCCGGGTT	GGCTACACCA	TCCACTATTT	CTCCGTAGAA						
2525	2530	2535	2540	2545	2550	2555	2560	2565	2570	2575	2580
TTCTAGAGAC	ACATTGGACC	AGATGAGGAT	CCGAAACGGC	AGCCTTTACG	TTTCATCACCT						
AAGATCTCTG	TGTAACCTGG	TCTACTCCTA	GGCTTTGCCG	TGGGAAATGC	AAGTAGTGGA						
2585	2590	2595	2600	2605	2610	2615	2620	2625	2630	2635	2640
GCTAGAACCT	CTCGTAGTCC	ATCACCATT	CTTGGCATTG	GAATTCCTACT	GGAAAAAAT						
CGATCTTGGG	GAGCATCAGG	TAGTGGTAAA	GAACCGTAAC	CTTAAGATGA	CCTTTTTTTTA						
2645	2650	2655	2660	2665	2670	2675	2680	2685	2690	2695	2700
ACAAAAAGCA	AAACAAAACC	CTCAGCACTG	TTACAAGAGG	CCATTTAAGT	ATCTTGTTGCT						
TGTTTTTTCGT	TTTGTTTTGG	GAGTCGTGAC	AATGTTCTCC	GGTAAATTCA	TAGAACACGA						
2705	2710	2715	2720	2725	2730	2735	2740	2745	2750	2755	2760
TCTTCACCTA	CCCATTAGCC	AGGTTCTCAT	TAGGTTTTTGC	TTGGGCCTCC	CTGGCACTGA						
AGAAGTGAAT	GGGTAATCGG	TCCAAGAGTA	ATCCAAAACG	AACCCGGAGG	GACCGTGACT						
2765	2770	2775	2780	2785	2790	2795	2800	2805	2810	2815	2820
ACCTTAGGGCT	TTGTATGACA	GTGAAGCAGC	ACTGTGAGTG	GTTCAAGCAC	ACTGGAATAT						
TGGAATCCGA	AACATACTGT	CACCTCGTGG	TGACACTCAC	CAAGTTCGTG	TGACCTTATA						
2825	2830	2835	2840	2845	2850	2855	2860	2865	2870	2875	2880
AAAACAGTCA	TGGCCTGAGA	TGCAGGTGAT	GCCATTACAG	AACCAAATCG	TGGCACGTAT						
TTTTGTTCAGT	ACCGGACTCT	ACGTCCACTA	CGGTAATGTC	TTGGTTTAGC	ACCGTGCATA						
2885	2890	2895	2900	2905	2910	2915	2920	2925	2930	2935	2940
TGCTGTGTCT	CCTCTCAGAG	TGACAGTCAT	AAATACTGTC	AAACAATAAA	GGGAGAATGG						
ACGACACAGA	GGAGAGTCTC	ACTGTGAGTA	TTTATGACAG	TTTGTATTAT	CCTCTTTACC						
2945	2950	2955	2960	2965	2970	2975	2980	2985	2990	2995	3000
TGCTGTTTTAA	AGTCACATCC	CTGTAAATTG	CAGAAITCAA	AAGTGATTAT	CTCTTTGATC						
ACGACAAATT	TCAGTGTAGG	GACATTTAAC	GTCTTAAGTT	TTCACTAATA	GAGAACTAG						
3005	3010	3015	3020	3025	3030	3035	3040	3045	3050	3055	3060
TACTTGCCTC	ATTTCCCTAT	CTTCTCCCCC	ACGGTATCCT	AAACTTTAGA	CTTCCCACTG						
ATGAACGGAG	TAAAGGGATA	GAAGAGGGGG	TGCCATAGGA	TTTGAAATCT	GAAGGGTGAC						
3065	3070	3075	3080	3085	3090	3095	3100	3105	3110	3115	3120

FIG. 8E

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TTCTGAAAGG AGACATTGCT CTATGTCTGC CTTCGACCAC AGCAAGCCAT CATCCTCCAT
AAGACTTTCC TCTGTAACGA GATACAGACG GAAGCTGGTG TCGTTCCGTA GTAGGAGGTA

3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180
* * * * *
TGCTCCCGGG GACTCAAGAG GAATCTGTTT CTCTGCTGTC AACTTCCCAT CTGGCTCAGC
ACGAGGGCCC CTGAGTTCTC CTTAGACAAA GAGACGACAG TTGAAGGGTA GACCGAGTCG

3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240
* * * * *
ATAGGGTCAC TTTGCCATTA TGCAAATGGA GATAAAAGCA ATTCTGGCTG TCCAGGAGCT
TATCCCAAGT AAACGGTAAT ACGTTTACCT CTATTTTCGT TAAGACCGAC AGGTCTCTGA

3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300
* * * * *
AATCTGACCG TTCTATTGTG TGGATGACCA CATAAGAAGG CAATTTTAGT GTATTAATCA
TTAGACTGGC AAGATAACAC ACCTACTGGT GTATTCTTCC GTTAAATCA CATAATTAGT

3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360
* * * * *
TAGATTATTA TAAACTATAA ACTTAAGGGC AAGGAGTTTA TTACAATGTA TCTTTATTAA
ATCTAATAAT ATTGATATT TGAATTCCTG TTCTCAAAT AATGTTACAT AGAAATAATT

3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420
* * * * *
AACAAAAGGG TGTATAGTGT TCACAAACTG TGAAAATAGT GTAAGAACTG TACATTGTGA
TTGTTTTCCC ACATATCACA AGTGTTTGAC ACTTTTATCA CATTCTTGAC ATGTAACACT

3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480
* * * * *
GCTCTGGTTA TTTTCTCTTT GTACCATAGA AAAATGTATA AAAATTATCA AAAAGCTAAT
CGAGACCAAT AAAAAGAGAA CATGGTATCT TTTTACATAT TTTTAATAGT TTTTCGATTA

3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540
* * * * *
GTGCAGGGAT ATTGCCTTAT TTGTCTGTAA AAAATGGAGC TCAGTAACAT AACTGCTTCT
CACGTCCCTA TAACGGAATA AACAGACATT TTTTACCTCG AGTCATTGTA TTGACGAAGA

3545 3550 3555 3560 3565 3570 3575
* * * * *
TGGAGCTTTG GAATATTTTA TCCTGTATTC TTGTTT (SEQ ID NO:9)
ACCTCGAAAC CTTATAAAAT AGGACATAAG AACAAA

```

FIG. 8F

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1
 MKK7
 HEP
 MKK1
 MKK2
 MKK3
 MKK4
 MKK5
 MKK6
 Consensus

70
 <SASSSSSSASAFASAPATGTFGGTYPTPTTRVSRATPTLPLSSSGGGLNRTRPVLP.PT.PHPPV
 MPKKKP--TPIQ.NPA-PDGSVANG
 MLARRKPVLP.A.TINP.IAEGP.PT.
 MSKPPA-----PN.TPPRN
 MAAPSPSGGGGGSGTGPVGPAPGHPAVSSMQGRKALKLNFNANPPFKSTARFTLNPN.TGVQN
 <IGQVLPEATTTAFEYEDGDRITVRSDEEMKAMLSYYYSTVNEQQVNGQLIEP.QIFPRACK.PGERN
 MSQSKGKKRNPGLKIPKEAEQFQ-----TSSTPPRD

71
 MKK7
 HEP
 MKK1
 MKK2
 MKK3
 MKK4
 MKK5
 MKK6
 Consensus

140
 I
 IEIDQKLQEIIMQT-GYLTIG-----GQRYQAEI-----NDLENLGEMSGTCGQVWKMFR
 S.T.M..KI..E..K.N.N-----RQ.PTD.-----KH..DL.N..S.N.V..MHL
 TSSAETNL.ALQKLEE.ELDE-----Q..KRL.AFLTQKQKVGELKDD.F.KIS.L.A.NG.V.F.VSHK
 EGASEANLVDLQKLEE.ELDE-----Q..KRL.AFLTQKQKVGELKDD.F.RIS.L.A.NG.V.T.VQH.
 -----LDSR-TFI..G-----DRNFEV.A-----D..VTIS.L.R.AY.V.E.V.HA
 PH.ERLRTHSISS--K.K.SP-----E.HWDFTA-----E..KD...I.R.AY.S.N..VHK
 .HGLKVNTRAGPSQHSSPAVSDSLPSNLKKSSAELKKILANGQMNEQ.IRYRDTL.H.NG.T.Y.AYHV
 -----LDSK-ACIS.G-----N.NFEVKA-----D..L.PIM.L.R.AY.V.E...HV
 D G G G V K

141
 MKK7
 HEP
 MKK1
 MKK2
 MKK3
 MKK4
 MKK5
 MKK6
 Consensus

210
 V
 KTGHIIAVKOMRRSGNKEENKRILMDLDVVLKSHDCPYIVQCFCGTFITNTDVFIAEMLM-GTCAEKLKK-
 SSNT.....T..A.....K...K.L.C.VRDP..W.C....-SM.FD..L.-
 PS.LVM.R.LIHLEIKPAIRNQ.IRE.Q.-.HECNSP...GFY.A.YSDGEIS.C..H.D.GSLDQVL.K
 PS.L.M.R.LIHLEIKPAIRNQ.IRE.Q.-.HECNSP...GFY.A.YSDGEIS.C..H.D.GSLDQVL.E
 QS.T.M...RI.A.V.SQ.Q..LI...INMRTV..F.T.TFY.ALFREG..W.C....D-.SLD.FYRK
 PS.Q.M...RI.S.VDEK.Q.QLJ.....MRSS.....FY.ALFREG.CW.C....-S.SFD.FY.Y
 PS.K.L...VILLDTL.LQ.Q.MSE.EILI.-C.SS..IGFY.A.FVENRIS.CTEF.D.GSLDDIG.-
 PS.Q.M...RI.A.V.SQ.Q..LL....ISMRTV...FTVTFY.ALFREG..W.C....-D-.SLD.FY.Q
 I A K I M G

FIG. 9A

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MKK7	211	VI	280
HEP	---	RMQGP	PERILGKMTVAIVKALYYLKEKHGVIHRDVKPSNILLDERGQIKLCDFGISGRIVDSKAKT
MKK1	---	LSKK.V.Q.	...T.N.S...D...I...N...N...
MKK2	---	A.R.Q.	...VSI.VIKG.T.R...KIM...VNS.E...V.Q.I..M.NS
MKK3	---	AKR...E...	...VSI.VIRG.A.R...QIM...VNS.E...V.Q.I..M.NS
MKK4	---	VLDK-NMT...	...D.EIA.S.R.EH.HS.LS.I...V.INKE.HV.M...Y...V...
MKK5	---	VYSVLDV...	...E...I.L.T.K.NH...NLKII...I...DRS.N...Q...I...
MKK6	---	---	...M.HV.RIA..V.KG.T.WS-LKIL...M.VNT...V...V.TQ..N.I...
Consensus	---	VIDK-GQT...	...D...IA.S...EH.HS.LS.I...V.INAL..V.M...Y...V...
		PE ILG	I L HRD KPSN L G K CDFG S LV S A
MKK7	281	VIII	350
HEP	---	RSAGCAAYMAPERIDPPDP	TKPDYDIRADVWSLISLVELATGQFPYKNCKTD---
MKK1	---	---	...K.K...T...ARS.EG.N...
MKK2	---	F-V.TRS.S...	...LQGT...SVQS.I.M.L...M.V.RY.IPPDAKELELMFGCQV---EGD
MKK3	---	F-V.TRS...	...LQGT...SVQS.I.M.L...V.RY.IPPDAKELEAIFGRPVVDGEEGE
MKK4	---	MD...KP...	...N-ELNQG.NVKS...TMI.M.ILR...ESWG.P---
MKK5	---	---	...D...RP...SASRQG.V.S...T.Y...R...PKWNSV---
MKK6	---	Y-V.TN...	...SSEQ...G.HS...FM.IQKN.GSLMP---
Consensus	---	ID...KP...	...N-ELNQG.SVKS.I...TMI...ILR...DSWG.P---
		G YM PER	Y D WSLG E
MKK7	351	X	420
HEP	---	---	...FEVLTKVQEEPLP-G-HMGFSGDFQSEVKDCLTKDHRKR
MKK1	---	---	...DS...C.Y.EGYN..QQ.RD..IK...N.OD.
MKK2	---	AAETPRPRTPGRPLSSYGMDSRPPMAI..L.DYIVN.P.K.S.V---	LE..D..NK..I.NPAE.
MKK3	---	PHSISPRPRPGRPVSGHGMDSRPAMAI..L.DYIVN.P.K.N.V---	TP...E..NK..I.NPAE.
MKK4	---	---	...QQ.KQ.VE.PS.Q..AD---R..PE.VD.TAQ..R.NPAE.
MKK5	---	---	...DQ..Q.VKGD..Q.SNSEERE..PS.IN..NL...ES...
MKK6	---	---	...LQL.QCIVD.DS.V..V.E---EP.VH.ITQ.MR.QPKE.
Consensus	---	---	...QQ.KQ.V...S.Q..AD---K..AE.VD.TSQ..K.NSKE.
		L P L	F CL K R
MKK7	421	XI	473
HEP	---	PKYNKLLHSEFIKHYEILEVDVAS-WFKDVMAKTESPRTSGVLSQLHLPFFR	(SEQ ID NO: 18)
MKK1	---	...PE..AQP..RI..SAK...PN---QSI---DNRL..AN.DPTLQR..NS	(SEQ ID NO: 21)
MKK2	---	ADLKQ.MV.A...RSDAE...F.G-.LCSTIGLNQNPSTPTTHAGV	(SEQ ID NO: 11)
MKK3	---	ADLKM.TN.T...RS.VE...F.G-.LCKTLRLNQPPTPTTRAV	(SEQ ID NO: 12)
MKK4	---	MS.LE.M..P.FTLHKTKKT.I.A-FV.KILGEDS	(SEQ ID NO: 2)
MKK5	---	...KE..K.P..LMY.ERA.E..C-YVCKILDQMPATP.SPMYVD	(SEQ ID NO: 10)
MKK6	---	.APEE.MG.P..VQFNDGNAA.VSM.VCRALERRTSRGPRAAAGH	(SEQ ID NO: 22)
Consensus	---	.T.PE.MQ.P.FTLH.SKGT....-EVKLILGD	(SEQ ID NO: 4)
		L F	(SEQ ID NO: 27)

FIG. 9B

MKK7

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Sequence Range: 1 to 1623

```

      10      20      30      40      50      60
      *      *      *      *      *      *
GGAAAGGCAG CCTCCTGTAG GTGAAAATTC TGTTCACCTAC CTGGCCACCT GGCCTGACTG
CCTTTCCGTC GGAGGACATC CACTTTTAAG ACAAGTGATG GACCGGTGGA CCGGACTGAC

      70      80      90     100     110     120
      *      *      *      *      *      *
ACCTTCACAG CTTGATCATC TTCTGAAGA GGCATTCAGG ATTCCCTCCA TCCCTACCCC
TGAAGTGTC GAAGTACTAG AAGGACTTCT CCGTAAGTCC TAAGGGAGGT AGGGATGGGG

     130     140     150     160     170     180
      *      *      *      *      *      *
TTCTGGACAA AGTCTTCACAG GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATACC
AAGACCTGTT TCAGAAGGTG CAAAGGAAGG ACCCTCAAAG AAGGTCTTG ACCTCTATGG

     190     200     210     220     230     240
      *      *      *      *      *      *
CAGAGCCCTG CAACTCCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT COTCAGAGAG
GTCTCGGGAC GTTGAGGGTG ACCGGTTGCT ACCCCCGTCG GCGAGTGGTA GGAGTCTCTC

     250     260     270     280     290
      *      *      *      *      *
CTCCCCACAG CACCCTACAC CCCCCACCCG GCCCCGCCAC ATG CTG GGG CTC CCA
GAGGGGTGTC GTGGGATGTG GGGGGTGGGC CGGGGCGGTG TAC GAC CCC GAG GGT
                                   Met Leu Gly Leu Pro>

```

```

     300     310     320     330     340
      *      *      *      *      *
TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG
AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG CTC TAA CTG GTC
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln>

```

```

     350     360     370     380     390
      *      *      *      *      *
AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC
TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC TGA TAG CCC CCG
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly>

```

```

     400     410     420     430
      *      *      *      *
CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG
GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG AAC CCA CTC TAC
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met>

```

```

    440     450     460     470     480
      *      *      *      *      *
GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA
CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCG AAG GCC TTC TGT
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr>

```

```

    490     500     510     520     530
      *      *      *      *      *
GGC CAC ATC ATT GCT GTT AAG CAA ATG CCG CGC TCT GGG AAC AAG GAA
CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA CCC TTG TTC CTT
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu

```

FIG. 10A

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540	550	560	570	580
GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG ACC CAT				
CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT GAG TTC TCG GTA				
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His>				
590	600	610	620	630
GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA				
CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG TAG TGG TTG TGT				
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr>				
640	650	660	670	
GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG				
CTG CAG AAA TAA CCG TAC CTC GAG TAC CCG TGT ACA CGT CTC TTC GAC				
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu>				
680	690	700	710	720
AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG ATG				
TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG GAC CCG TTC TAC				
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met>				
730	740	750	760	770
ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC				
TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC CTC TTC GTA CCG				
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly>				
780	790	800	810	820
GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CGG				
CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC GAT CTA CTC GCC				
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg>				
830	840	850	860	870
GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC				
CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG GCG GAA CAA CTG				
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp>				
880	890	900	910	
TCC AAA GCG AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC				
AGG TTT CCG TTT TGT GCC TCA CGA CCG ACA CGA CCG ATA TAC CGA GGG				
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro>				
920	930	940	950	960
GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA				
CTC GCG TAG CTG GGA GGT CTA GGG TGG TTG GGA CTG ATA CTG TAG GCT				
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg>				

FIG. 10B

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MKK7

```

970      980      990      1000      1010
*      *      *      *      *
GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA
CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC GAC CGT TGT CCT
Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly>

1020      1030      1040      1050      1060
*      *      *      *      *
CAG TTC CCC TAT AAG AAC TCC AAG ACG GAC TTT GAG GTC CTC ACC AAA
GTC AAG GGG ATA TTC TTG ACG TTC TCC CTG AAA CTC CAG GAG TCG TTT
Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys>

1070      1080      1090      1100      1110
*      *      *      *      *
GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA
CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG TAC CCG AAG AGT
Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser>

1120      1130      1140      1150
*      *      *      *
GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG
CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA TTT CTA GTG TCC
Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg>

1160      1170      1180      1190      1200
*      *      *      *      *
AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC AAG CAC
TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG AAG TAG TTC GTG
Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His>

1210      1220      1230      1240      1250
*      *      *      *      *
TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC ATG
ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA TTC CTA CAG TAC
Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met>

1260      1270      1280      1290      1300
*      *      *      *      *
GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC CAT
CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC TCA GTC GTG GTA
Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His>

1310      1320      1330      1340      1350      1360
*      *      *      *      *      *
CTG CCC TTC TTC AGG TA GCCTCATGGC AGCGGCCAGC CCGCAGGGG CCGCGGGCCA
GAC GGG AAG AAG TCC AT CCGAGTACCG TCGCCGGTCG GGGCGTCCCC GGGGCCCCGT
Leu Pro Phe Phe Arg>

1370      1380      1390      1400      1410      1420
*      *      *      *      *      *
CGGCCACCGA CCCCCCCCCC AACCTGGCCA ACCCAGCTGC CCATCAGGGG ACCTGGGACC
GCGGTGGCT GGGGGGGGGG TTGGACCGGT TGGGTGGACG GGTAGTCCCC TGGACCCTGG

```

FIG. 10C

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MKK7

1430	1440	1450	1460	1470	1480
TGGACGACTG	CCAAGGACTG	AGGACAGAAA	GTAGGGGGTT	CCCATCCAGC	TGTGACTCCC
ACCTGCTGAC	GGTTCCTGAC	TCCTGTCTTT	CATCCCCCAA	GGGTAGGTCG	AGACTGAGGG
1490	1500	1510	1520	1530	1540
TGCCTACCAG	CTGTGGACAA	AAGGGCATGC	TGGTTCCTAA	TCCCTCCCAC	TGTGGGGTCA
ACGGATGGTC	GACACCTGTT	TTCCCCGTACG	ACCAAGGATT	AGGGAGGGTG	AGACCCCACT
1550	1560	1570	1580	1590	1600
GCCAGCAGTG	TGAGCCCCAT	CCCACCCCCA	CAGACACTGT	GAACGGAAGA	CAGCAGGCCA
CGGTCGTCAC	ACTCGGGGTA	GGGTGGGGCT	GTCTGTGACA	CTTGCCTTCT	GTCCGTCCGGT
1610	1620				
AAAAAAAAAA	AAAAAAAAAA	AAA			
AAAAAAAAAA	AAAAAAAAAA	AAA			

(SEQ ID NO: 17)

FIG. 10D

MKK7b
Sequence Range: 1 to 1465

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```

      10      20      30      40      50
      *      *      *      *      *
GC ACG AGC CCT GGT CCT GCG CCG TCC CAG CGA GCA GCG CTG CAA CTC CCA
CG TGC TCG GGA CGA GGA CCG GCG AGG GTC GCT CGT CCG GAC GTT GAG GGT
  Thr Ser Pro Ala Pro Ala Pro Ser Gln Arg Ala Ala Leu Gln Leu Pro>

      60      70      80      90
      *      *      *      *
CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA GAG AGC TCC CCA
GAC CCG TTG CTA CCC CCG TCG GCG AGT GGT AGG AGT CTC TCG AGG GGT
Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro>

    100      110      120      130      140
      *      *      *      *      *
CAG CAC CCT ACA CCC CCC ACC CCG CCC CGC CAC ATG CTG GCG CTC CCA
GTC GTG GGA TGT GGG GGG TGG GCC GCG GTG TAC GAC CCC GAG GGT
Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu Pro>

    150      160      170      180      190
      *      *      *      *      *
TCA ACC TTG TTC ACA CCG CCG AGT ATG GAG AGC ATC GAG ATT GAC CAG
AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG CTC TAA CTG GTC
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln>

    200      210      220      230      240
      *      *      *      *      *
AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC
TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC TGA TAG CCC CCG
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly>

    250      260      270      280      290
      *      *      *      *      *
CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG
GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG AAC CCA CTC TAC
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met>

    300      310      320      330
      *      *      *      *
GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CCG TTC CCG AAG ACA
CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCG AAG GCC TTC TGT
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr>

    340      350      360      370      380
      *      *      *      *      *
GGC CAC ATC ATT GCT GTT AAG CAA ATG CCG CCG TCT CCG AAC AAG GAA
CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA CCC TTG TTC CTT
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu>

    390      400      410      420      430
      *      *      *      *      *
GAG AAT AAG CCG ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT
CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT GAG TTC TCG GTA
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His>

```

FIG. 11A

37/54

MKK7b

```

      440      450      460      470      480
      *      *      *      *      *
GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA
CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG TAG TGG TTG TGT
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr>

      490      500      510      520      530
      *      *      *      *      *
GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG
CTG CAG AAA TAA CCG TAC CTC GAG TAC CCG TGT ACA CGT CTC TTC GAC
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu>

      540      550      560      570
      *      *      *      *
AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG ATG
TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG GAC CCG TTC TAC
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met>

580      590      600      610      620
      *      *      *      *      *
ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC
TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC CTC TTC GTA CCG
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly>

      630      640      650      660      670
      *      *      *      *      *
GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CCG
CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC GAT CTA CTC GCC
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg>

      680      690      700      710      720
      *      *      *      *      *
GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC
CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG GCG GAA CAA CTG
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp>

      730      740      750      760      770
      *      *      *      *      *
TCC AAA GCC AAA ACA CCG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC
AGG TTT CCG TTT TGT GCC TCA CGA CCG ACA CGA CCG ATA TAC CGA GGG
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro>

      780      790      800      810
      *      *      *      *
GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA
CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG ATA CTG TAG GCT
Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg>

```

FIG. 11B

MKK7b 38/54

820 830 840 850 860
 GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA
 CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC GAC CGT TGT CCG
 Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly>

870 880 890 900 910
 CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC AAA
 GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC CAG GAG TGG TTT
 Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys>

920 930 940 950 960
 GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA
 CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG TAC CCG AAG AGT
 Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser>

970 980 990 1000 1010
 GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG
 CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA TTT CTA GTG TCC
 Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg>

1020 1030 1040 1050
 AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC AAG CAC
 TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG AAG TAG TTC GTG
 Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His>

1060 1070 1080 1090 1100
 TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC ATG
 ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA TTC CTA CAG TAC
 Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met>

1110 1120 1130 1140 1150
 GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC CAT
 CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC TCA GTC GTG GTA
 Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His>

1160 1170 1180 1190 1200 1210
 CTG CCC TTC TTC AGG T AGCCTCATGG CAGCGGCCAG CCCCAGAGGG GCGCCGGGCC
 GAC GGG AAG AAG TCC A TCGGAGTACC GTCCCGCGTC GGGGCGTCCC CGGGGCCCCG
 Leu Pro Phe Phe Arg> (SEQ ID NO: 20)

1220 1230 1240 1250 1260 1270
 ACGGCCACCG ACCCCCCCCC CAACCTGCCC AACCCAGCTG CCCATCAGGG GACCTGGGAC
 TCCCGGTGGC TGGGGGGGGG GTTGGACCGG TTGGGTGCGAC GGGTAGTCCC CTGGACCCCTG

1280 1290 1300 1310 1320 1330
 CTGGACGACT GCCAAGGACT GAGGACAGAA AGTAGGGGGT TCCCATCCAG CTCTGACTCC
 GACCTGCTGA CGGTTCCTGA CTCCTGTCTT TCATCCCCCA AGGGTAGGTC GAGACTGAGG

FIG. 11C

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MKK7b

```
      1340      1350      1360      1370      1380      1390
      *          *          *          *          *          *
CTGCCTACCA GCTGTGGACA AAAGGGCATG CTGGTTCCTA ATCCCTCCCA CTCTGGGGTC
GACGGATGGT CGACACCTGT TTTCCCGTAC GACCAAGGAT TAGGGAGGGT GAGACCCCAAG

      1400      1410      1420      1430      1440      1450
      *          *          *          *          *          *
AGCCAGCAGT GTGAGCCCCA TCCCACCCCG ACAGACACTG TGAACGGAAG ACAGCAAAAA
TCGGTCGTCA CACTCGGGGT AGGGTGGGGC TGTCTGTGAC ACTTGCCTTC TGTCTGTTTTT

      1460
      *          *
AAAAAAAAAA AAAAA (SEQ ID NO: 19)
TTTTTTTTTT TTTT
```

FIG. 11D

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Human MKK7
Sequence Range: 1 to 843

```

      10      20      30      40      50      60
      *      *      *      *      *      *
TGTTTGTCTG CCGGACTGAC GGGCGGGCCGG GCGGTGCGCG GCGGCGGTGG CCGCGGGGAA
ACAAACAGAC GGCCTGACTG CCGCGCGGCC CGCCACGCGC CGCCGCCACC GCCGCCCTT

      70      80      90      100
      *      *      *      *
G ATG GCG GCG TCC TCC CTG GAA CAG AAG CTG TCC CGC CTG GAA GCA AAG
C TAC CGC CGC AGG AGG GAC CTT GTC TTC GAC AGG GCG GAC CTT CGT TTC
Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys>

110      120      130      140      150
      *      *      *      *      *
CTG AAG CAG GAG AAC CGG GAG GCC CGG CGG AGG ATC GAC CTC AAC CTG
GAC TTC GTC GGG GTC GCC CTC CGG GCC GCC TCC TAG CTG GAG TTG GAC
Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu>

160      170      180      190      200
      *      *      *      *      *
GAT ATC AGC CCC CAG CGG CCC AGG CCC ACC CTG CAG CTC CCG CTG GCC
CTA TAG TCG GGG GTC GCC GGG TCC GGG TGG GAC GTC GAG GGC GAC CGG
Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala>

210      220      230      240      250
      *      *      *      *      *
AAC GAT GGG GGC AGC CGC TCG CCA TCC TCA GAG AGC TCC CCG CAG CAC
TTG CTA CCC CCG TCG GCG AGC GGT AGG AGT CTC TCG AGG GGC GTC GTG
Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His>

260      270      280      290      300
      *      *      *      *      *
CCC ACG CCC CCC GCC CGG CCC CGC CAC ATG CTG GGG CTC CCG TCA ACC
GGG TGC GGG GGG CGG GCC GGG GCG GTG TAC GAC CCC GAG GGC AGT TGG
Pro Thr Pro Pro Ala Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr>

310      320      330      340
      *      *      *      *
CTG TTC ACA CCC CGC AGC ATG GAG AGC ATT GAG ATT GAC CAG AAG CTG
GAC AAG TGT GGG GCG TCG TAC CTC TCG TAA CTC TAA CTG GTC TTC GAC
Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu>

350      360      370      380      390
      *      *      *      *      *
CAG GAG ATC ATG AAG CAG ACG GGC TAC CTG ACC ATC GGG GGC CAG CGC
GTC CTC TAG TAC TTC GTC TGC CCG ATG GAC TGG TAG CCC CCG GTC GCG
Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg>

400      410      420      430      440
      *      *      *      *      *
TAC CAG GCA GAA ATC AAC GAC CTG GAG AAC TTG GGC GAG ATG GGC AGC
ATG GTC CGT CTT TAG TTG CTG GAC CTC TTG AAC CCG CTC TAC CCG TCG
Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser>

```

FIG. 12A

Human MKK7

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```

      450          460          470          480          490
      *            *            *            *            *
GGC ACC TGC GGC CAG GTG TGG AAG ATG CGC TTC CGG AAG ACC GGC CAC
CCG TGG ACG CCG GTC CAC ACC TTC TAC GCG AAG GCC TTC TGG CCG GTG
Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His>

      500          510          520          530          540
      *            *            *            *            *
GTC ATT GCC GTT AAG CAA ATG CGG CGC TCC GGG AAC AAG GAG GAG AAC
CAG TAA CCG CAA TTC GTT TAC GCC GCG AGG CCC TTG TTC CTC CTC TTG
Val Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn>

      550          560          570          580
      *            *            *            *            *
AAG CGC ATC CTC ATG GAC CTG GAT GTG GTG CTG AAG AGC CAC GAC TGC
TTC GCG TAG GAG TAC CTG GAC CTA CAC CAC GAC TTC TCG GTG CTG ACG
Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys>

590          600          610          620          630
*            *            *            *            *
CCC TAC ATC GTG CAG TGC TTT GGG ACG TTC ATC ACC AAC ACG GAC GTC
GGG ATG TAG CAC GTC ACG AAA CCC TGC AAG TAG TGG TTG TGC CTG CAG
Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val>

      640          650          660          670          680
      *            *            *            *            *
TTC ATC GCC ATG GAG CTC ATG GGC ACC TGC GCT GAG AAG CTC AAG AAG
AAG TAG CCG TAC CTC GAG TAC CCG TGG ACG CGA CTC TTC GAG TTC TTC
Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys>

      690          700          710          720          730
      *            *            *            *            *
CGG ATG CAG GGC CCC ATC CCC GAG CGC ATT CTG GGC AAG ATG ACA GTG
GCC TAC GTC CCG GGG TAG GGG CTC GCG TAA GAC CCG TTC TAC TGT CAC
Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val>

      740          750          760          770          780
      *            *            *            *            *
GCG ATT GTG AAG GCG CTG TAC TAC CTG AAG GAG AAG CAC GGT GTC ATC
CGC TAA CAC TTC CGC GAC ATG ATG GAC TTC CTC TTC GTG CCA CAG TAG
Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile>

      790          800          810          820
      *            *            *            *            *
CAC CGC GAC GTC AAG CCC TCC AAC ATC CTG CTG GAC GAG CGG GGC CAG
GTG GCG CTG CAG TTC GGG AGG TTG TAG GAC GAC CTG CTC GCC CCG GTC
His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln>

830          840
*            *
ATC AAG CTC TGC GA (SEQ ID NO: 25)
TAG TTC GAG ACG CT
Ile Lys Leu Cys> (SEQ ID NO: 26)

```

FIG. 12B

Mouse MKK7c

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Sequence Range: 1 to 1643

```

      10      20      30      40      50      60
      *      *      *      *      *      *
AGCGCAGGCG CAGTGCGGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG
TCGCGTCCGC GTCACGCCAC AAACAGATGG GGCCTGACTG CCCACCGGAC CCGCACTCGC

      70      80      90      100     110
      *      *      *      *      *
GCGGCAGCGG CCGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG
CGCCGTCGCC GCGCCCCCTT C TAC CGC CGC AGG AGG GAC CTC GTC TTC GAC
                      Met Ala Ala Ser Ser Leu Glu Gln Lys Leu>

      120     130     140     150
      *      *      *      *
TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG
AGG GCG GAC CTT CGG TTC GAC TTC GTC CTC TTG GCA CTC CGG GCG TCC
Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg>

160      170      180      190      200
      *      *      *      *      *
AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC
TCC TAG CTG GAG TTG AAC CTA TAG TCG GGT GTC GCC GGG TCC GGG TGG
Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr>

210      220      230      240      250
      *      *      *      *      *
CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA
GAC GTT GAG GGT GAC CGG TTG CTA CCC CCG TCG GCG AGT GGT AGG AGT
Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser>

260      270      280      290      300
      *      *      *      *      *
GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG
CTC TCG AGG GGT GTC GTG GGA TGT GGG GGG TGG GCC GGG GCG GTG TAC
Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met>

310      320      330      340      350
      *      *      *      *      *
CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC
GAC CCC GAG GGT AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG
Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile>

360      370      380      390
      *      *      *      *
GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG
CTC TAA CTG GTC TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC
Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu>

400      410      420      430      440
      *      *      *      *      *
ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC
TGA TAG CCC CCG GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG
Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn>

```

FIG. 13A

43/54

Mouse MKK7c

```

450      460      470      480      490
*      *      *      *      *
TTG GGT GAG ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG
AAC CCA CTC TAC CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC
Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg>

500      510      520      530      540
*      *      *      *      *
TTC CGG AAG ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT
AAG GCC TTC TGT CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA
Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser>

550      560      570      580      590
*      *      *      *      *
GGG AAC AAG GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA
CCC TTG TTC CTT CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT
Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val>

600      610      620      630
*      *      *      *
CTC AAG AGC CAT GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC
GAG TTC TCG GTA CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG
Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe>

640      650      660      670      680
*      *      *      *      *
ATC ACC AAC ACA GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT
TAG TGG TTG TGT CTG CAG AAA TAA CCG TAC CTC GAG TAC CCG TGT ACA
Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys>

690      700      710      720      730
*      *      *      *      *
GCA GAG AAG CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC
CGT CTC TTC GAC TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG
Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile>

740      750      760      770      780
*      *      *      *      *
CTG GGC AAG ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG
GAC CCG TTC TAC TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC
Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys>

790      800      810      820      830
*      *      *      *      *
GAG AAG CAT GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG
CTC TTC GTA CCG CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC
Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu>

840      850      860      870
*      *      *      *
CTA GAT GAG CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC
GAT CTA CTC GCC CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG
Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly>

```

FIG. 13B

44/54

Mouse MKK7c

```

880      890      900      910      920
*      *      *      *      *
CGC CTT GTT GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC
GCG GAA CAA CTG AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG
Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala>

930      940      950      960      970
*      *      *      *      *
TAT ATG GCT CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC
ATA TAC CGA GGG CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG
Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp>

980      990      1000      1010      1020
*      *      *      *      *
TAT GAC ATC CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG
ATA CTG TAG GCT CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC
Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu>

1030      1040      1050      1060      1070
*      *      *      *      *
CTG GCA ACA GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG
GAC CGT TGT CCT GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC
Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu>

1080      1090      1100      1110
*      *      *      *
GTC CTC ACC AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC
CAG GAG TGG TTT CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG
Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His>

1120      1130      1140      1150      1160
*      *      *      *      *
ATG GGC TTC TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT
TAC CCG AAG AGT CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA
Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr>

1170      1180      1190      1200      1210
*      *      *      *      *
AAA GAT CAC AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC
TTT CTA GTG TCC TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG
Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser>

1220      1230      1240      1250      1260
*      *      *      *      *
TTC ATC AAG CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT
AAG TAG TTC GTG ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA
Phe Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe>

1270      1280      1290      1300      1310
*      *      *      *      *
AAG GAT GTC ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG
TTC CTA CAG TAC CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC

```

FIG. 13C

45/54

Mouse MKK7c

Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu>

```

      1320      1330      1340      1350      1360
      *      *      *      *      *
AGT CAG CAC CAT CTG CCC TTC TTC AGG TA GCCTCATGGC AGCGGCCAGC
TCA GTC GTG GTA GAC GGG AAG AAG TCC AT CGGAGTACCG TCGCCGGTCG
Ser Gln His His Leu Pro Phe Phe Arg> (SEQ ID NO: 28)

      1370      1380      1390      1400      1410      1420
      *      *      *      *      *      *
CCCCCAGGGG CCCCCGGCCA CGGCCACCGA CCCCCCCCCC AACCTGGCCA ACCCAGCTGC
GGGCGTCCCC GGGGCCCCGT GCCGGTGGCT GGGGGGGGGG TTGGACCGGT TGGGTGACG
      1430      1440      1450      1460      1470      1480
      *      *      *      *      *      *
CCATCAGGGG ACCTGGGACC TGGACGACTG CCAAGGACTG AGGACAGAAA GTAGGGGGTT
GGTAGTCCCC TGGACCCCTGG ACCTGCTGAC GGTTCCTGAC TCCTGTCTTT CATCCCCAA
      1490      1500      1510      1520      1530      1540
      *      *      *      *      *      *
CCCATCCAGC TCTGACTCCC TGCCTACCAG CTGTGGACAA AAGGGCATGC TGGTTCCTAA
GGGTAGGTCT AGACTGAGGG ACGGATGGTC GACACCTGTT TTCCCGTACG ACCAAGGATT
      1550      1560      1570      1580      1590      1600
      *      *      *      *      *      *
TCCCTCCCAC TCTGGGGTCA GCCAGCAGTG TGAGCCCCAT CCCACCCCGA CAGACACTGT
AGGGAGGGTG AGACCCCACT CGGTCGTCAC ACTCGGGGTA GGGTGGGGCT GTCTGTGACA
      1610      1620      1630      1640
      *      *      *      *
GAACGGAAGA CAGCAGGCCA AAAAAAAAAA AAAAAAAAAA AAA (SEQ ID NO: 27)
CTTGCCCTCT GTCGTCCGGT TTTTTTTTTT TTTTTTTTTT TTT

```

FIG. 13D

MKK7d

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Sequence Range: 1 to 1578

```

      10      20      30      40      50      60
      *      *      *      *      *      *
GGAAAGGCAG CCTCCTGTAG GTGAAAATTC TGTTCACTAC CTGGCCACCT GGCCCTGACTG
CCTTTCCGTC GGAGGACATC CACTTTTAAG ACAAGTGATG GACCGGTGGA CCGGACTGAC

      70      80      90     100     110     120
      *      *      *      *      *      *
ACCTTCACAG CTTGATCATC TTCCTGAAGA GGCATTGAGG ATTCCCTCCA TCCCTACCCC
TGGAAGTGTC GAACTAGTAG AAGGACTTCT CCGTAAGTCC TAAGGGAGGT AGGGATGGGG

      130     140     150     160     170     180
      *      *      *      *      *      *
TTCTGGACAA AGTCTTCCAC GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATACC
AAGACCTGTT TCAGAAGGTG CAAAGGAAGG ACCCTCAAAG AAGGTCCTTG ACCTCTATGG

      190     200     210     220     230     240
      *      *      *      *      *      *
CAGAGCCCTG CAACTCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT CCTCAGAGAG
GTCTCGGGAC GTTGAGGGTG ACCGGTTGCT ACCCCCGTCG GCGAGTGGTA GGAGTCTCTC

      250     260     270     280     290
      *      *      *      *      *
CTCCCCACAG CACCCTACAC CCCCCACCCG GCCCCGCCAC ATG CTG GGG CTC CCA
GAGGGGTGTC GTGGGATGTG GGGGGTGGGC CGGGGCGGTG TAC GAC CCC GAG GGT
                                   Met Leu Gly Leu Pro>

      300     310     320     330     340
      *      *      *      *      *
TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG
AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG CTC TAA CTG GTC
Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln>

      350     360     370     380     390
      *      *      *      *      *
AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC
TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC TGA TAG CCC CCG
Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly>

      400     410     420     430
      *      *      *      *
CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG
GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG AAC CCA CTC TAC
Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met>

440      450      460      470      480
      *      *      *      *      *
GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA
CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC AAG GCC TTC TGT
Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr>

490      500      510      520      530
      *      *      *      *      *
GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG GAA
CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA CCC TTG TTC CTT
Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu>

```

FIG. 14A

47/54

MKK7d

```

540      550      560      570      580
*      *      *      *      *
GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT
CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT GAG TTC TCG GTA
Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His>

590      600      610      620      630
*      *      *      *      *
GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC ATC ACC AAC ACA
CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG TAG TGG TTG TGT
Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr>

640      650      660      670
*      *      *      *
GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT GCA GAG AAG CTG
CTG CAG AAA TAA CCG TAC CTC GAG TAC CCG TGT ACA CGT CTC TTC GAC
Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu>

680      690      700      710      720
*      *      *      *      *
AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG ATG
TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG GAC CCG TTC TAC
Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met>

730      740      750      760      770
*      *      *      *      *
ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT GGC
TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC CTC TTC GTA CCG
Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly>

780      790      800      810      820
*      *      *      *      *
GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG CGG
CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC GAT CTA CTC GCC
Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg>

830      840      850      860      870
*      *      *      *      *
GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT GAC
CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG GCG GAA CAA CTG
Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp>

880      890      900      910
*      *      *      *
TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT CCC
AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG ATA TAC CGA GGG
Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro>

920      930      940      950      960
*      *      *      *      *
GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC CGA
CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG ATA CTG TAG GCT

```

FIG. 14B

MKK7d

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Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg>

970 980 990 1000 1010
 * * * * *
 GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA GGA
 CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC GAC CGT TGT CCT
 Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly>

1020 1030 1040 1050 1060
 * * * * *
 CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC AAA
 GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC CAG GAG TGG TTT
 Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys>

1070 1080 1090 1100 1110
 * * * * *
 GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC TCA
 CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG TAC CCG AAG AGT
 Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser>

1120 1130 1140 1150
 * * * *
 GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC AGG
 CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA TTT CTA GTG TCC
 Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg>

1160 1170 1180 1190 1200
 * * * * *
 AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC ATC AAG
 TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG AAG TAG TAG TTC
 Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Ile Lys>

1210 1220 1230 1240 1250
 * * * * *
 CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC
 GTG ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC AAA TTC CTA CAG
 His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val>

1260 1270 1280 1290 1300
 * * * * *
 ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC
 TAC CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG GAC TCA GTC GTG
 Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His>

1310 1320 1330 1340 1350
 * * * * *
 CAT CTG CCC TTC TTC AGT GGG AGT CTG GAG GAG TCT CCC ACT TCC CCA
 GTA GAC GGG AAG AAG TCA CCC TCA GAC CTC CTC AGA GGG TGA AGG GGT
 His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser Pro Thr Ser Pro>

1360 1370 1380 1390
 * * * *
 CCT TCT CCC AAG TCC TTC CCT CTG TCA CCA GCC ATC CCT CAG GCC CAG

FIG. 14C

SUBSTITUTE SHEET (RULE 26)

MKK7d

49/54

GGA AGA GGG TTC AGG AAG GGA GAC AGT GGT CGG TAG GGA GTC CGG GTC
 Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile Pro Gln Ala Gln>

1400 1410 1420 1430 1440 1450
 * * * * * *
 GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG GTCCCACCCT
 CGT CTC ACC CAG AGC CCG TCC ATCCCTGGAC CTCACCGGAC CAGGGTGGGA
 Ala Glu Trp Val Ser Gly Arg> (SEQ ID NO: 30)

 1460 1470 1480 1490 1500 1510
 * * * * * *
 CTGACCTCCT CCTCAGGCCA CCAGTGTTCG CCTCTTCCCT TTTTAAAACA AAATACCCTT
 GACTGGAGGA GGAGTCCGGT GGTCAACAACG GGAGAAGGGA AAAATTTTGT TTTATGGGAA

 1520 1530 1540 1550 1560 1570
 * * * * * *
 GTTTGTAAAT CCTTAGACGC TTGAGAATAA AACCCCTTCCC TTTTCTTCG AAAAAAAAAA
 CAAACATTTA GGAATCTGCG AACTCTTATT TTGGGAAGGG AAAAGAAGGC TTTTTTTTTT

*
 AAAAAAAAA (SEQ ID NO: 29)
 TTTTTTTT

FIG. 14D

50/54

MKK7e
Sequence Range: 1 to 1598

```

      10      20      30      40      50      60
      *      *      *      *      *      *
AGCGCAGGCG CAGTGCAGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG
TCGCGTCCGC GTCACGCCAC AACAGATGG GGCCTGACTG CCCACCGGAC CGCCACTCGC

      70      80      90      100     110
      *      *      *      *      *
GCGGCAGCGG CGGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG
CGCCGTCGCC GCCGCCCCCTT C TAC CGC CGC AGG AGG GAC CTC GTC TTC GAC
                      Met Ala Ala Ser Ser Leu Glu Gln Lys Leu>

      120     130     140     150
      *      *      *      *
TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG
AGG GCG GAC CTT CGG TTC GAC TTC GTC CTC TTG GCA CTC CGG GCG TCC
Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg>

160      170      180      190      200
*      *      *      *      *
AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC
TCC TAG CTG GAG TTG AAC CTA TAG TCG GGT GTC GCC GGG TCC GGG TGG
Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr>

      210     220     230     240     250
      *      *      *      *      *
CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA
GAC GTT GAG GGT GAC CGG TTG CTA CCC CCG TCG GCG AGT GGT AGG AGT
Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser>

      260     270     280     290     300
      *      *      *      *      *
GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG
CTC TCG AGG GGT GTC GTG GGA TGT GGG GGG TGG GCC GGG GCG GTG TAC
Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met>

      310     320     330     340     350
      *      *      *      *      *
CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC
GAC CCC GAG GGT AGT TGG AAC AAG TGT GGC GCG TCA TAC CTC TCG TAG
Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile>

      360     370     380     390
      *      *      *      *
GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG
CTC TAA CTG GTC TTC GAC GTC CTC TAG TAC TTC GTC TGT CCC ATG GAC
Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu>

400      410      420      430      440
*      *      *      *      *
ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC
TGA TAG CCC CCG GTC GCA ATA GTC CGT CTT TAG TTA CTG AAC CTC TTG
Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn>

```

FIG. 15A

Mouse MKK7e

51/54

```

450          460          470          480          490
*           *           *           *           *
TTG GGT GAG ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG
AAC CCA CTC TAC CCG TCA CCA TGG ACA CCA GTC CAC ACC TTC TAC GCC
Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg>

500          510          520          530          540
*           *           *           *           *
TTC CGG AAG ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT
AAG GCC TTC TGT CCG GTG TAG TAA CGA CAA TTC GTT TAC GCC GCG AGA
Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser>

550          560          570          580          590
*           *           *           *           *
GGG AAC AAG GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA
CCC TTG TTC CTT CTC TTA TTC GCG TAA AAC TAC CTG GAC CTA CAT CAT
Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val>

600          610          620          630
*           *           *           *
CTC AAG AGC CAT GAC TGC CCT TAC ATC GTT CAG TGC TTT GGC ACC TTC
GAG TTC TCG GTA CTG ACG GGA ATG TAG CAA GTC ACG AAA CCG TGG AAG
Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe>

640          650          660          670          680
*           *           *           *           *
ATC ACC AAC ACA GAC GTC TTT ATT GCC ATG GAG CTC ATG GGC ACA TGT
TAG TGG TTG TGT CTG CAG AAA TAA CGG TAC CTC GAG TAC CCG TGT ACA
Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr Cys>

690          700          710          720          730
*           *           *           *           *
GCA GAG AAG CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC
CGT CTC TTC GAC TTC TTT GCT TAC GTC CCG GGG TAA GGT CTC GCT TAG
Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile>

740          750          760          770          780
*           *           *           *           *
CTG GGC AAG ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG
GAC CCG TTC TAC TGA CAC CGC TAA CAC TTT CGT GAC ATG ATA GAC TTC
Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys>

790          800          810          820          830
*           *           *           *           *
GAG AAG CAT GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG
CTC TTC GTA CCG CAG TAG GTA GCG CTA CAG TTT GGG AGG TTG TAG GAC
Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu>

840          850          860          870
*           *           *           *
CTA GAT GAG CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC
GAT CTA CTC GCC CCG GTC TAG TTC GAG ACA CTG AAA CCG TAG TCA CCG
Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly>

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FIG. 15B

52/54

Mouse MKK7e

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880      890      900      910      920
*      *      *      *      *
CGC CTT GTT GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC
GCG GAA CAA CTG AGG TTT CGG TTT TGT GCC TCA CGA CCG ACA CGA CGG
Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala>

930      940      950      960      970
*      *      *      *      *
TAT ATG GCT CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC
ATA TAC CGA GGG CTC GCG TAG CTG GGA GGT CTA GGG TGG TTC GGA CTG
Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp>

980      990      1000      1010      1020
*      *      *      *      *
TAT GAC ATC CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG
ATA CTG TAG GCT CGA CTA CAC ACC TCG GAC CCG TAG AGT GAC CAC CTC
Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu>

1030      1040      1050      1060      1070
*      *      *      *      *
CTG GCA ACA GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG
GAC CGT TGT CCT GTC AAG GGG ATA TTC TTG ACG TTC TGC CTG AAA CTC
Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu>

1080      1090      1100      1110
*      *      *      *
GTC CTC ACC AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC
CAG GAG TGG TTT CAG GAT GTC CTT CTC GGG GGT GAG GAC GGA CCA GTG
Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His>

1120      1130      1140      1150      1160
*      *      *      *      *
ATG GGC TTC TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT
TAC CCG AAG AGT CCC CTG AAG GTC AGT AAA CAG TTT CTG ACG GAA TGA
Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr>

1170      1180      1190      1200      1210
*      *      *      *      *
AAA GAT CAC AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC
TTT CTA GTG TCC TTC TCT GGT TTC ATA TTA TTC GAT GAA CTT GTG TCG
Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser>

1220      1230      1240      1250      1260
*      *      *      *      *
TTC ATC ATC AAG CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG
AAG TAG TAG TTC GTG ATA CTC TAT GAG CTC CAC CTA CAG CGC AGG ACC
Phe Ile Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp>

1270      1280      1290      1300      1310
*      *      *      *      *
TTT AAG GAT GTC ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC
AAA TTC CTA CAG TAC CGC TTC TGG CTC AGG GGT TCC TGA TCA CCT CAG

```

FIG. 15C

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Mouse MKK7e

Phe Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val>

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      1320      1330      1340      1350
      *      *      *      *      *      *
CTG AGT CAG CAC CAT CTG CCC TTC TTC AGT GGG AGT CTG GAG GAG TCT
GAC TCA GTC GTG GTA GAC GGG AAG AAG TCA CCC TCA GAC CTC CTC AGA
Leu Ser Gln His His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser>

1360      1370      1380      1390      1400
      *      *      *      *      *      *
CCC ACT TCC CCA CCT TCT CCC AAG TCC TTC CCT CTG TCA CCA GCC ATC
GGG TGA AGG GGT GGA AGA GGG TTC AGG AAG GGA GAC AGT GGT CGG TAG
Pro Thr Ser Pro Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile>

1410      1420      1430      1440      1450      1460
      *      *      *      *      *      *
CCT CAG GCC CAG GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG
GGA GTC CGG GTC CGT CTC ACC CAG AGC CCG TCC ATCCCTGGAC CTCACCGGAC
Pro Gln Ala Gln Ala Glu Trp Val Ser Gly Arg> (SEQ ID NO: 32)

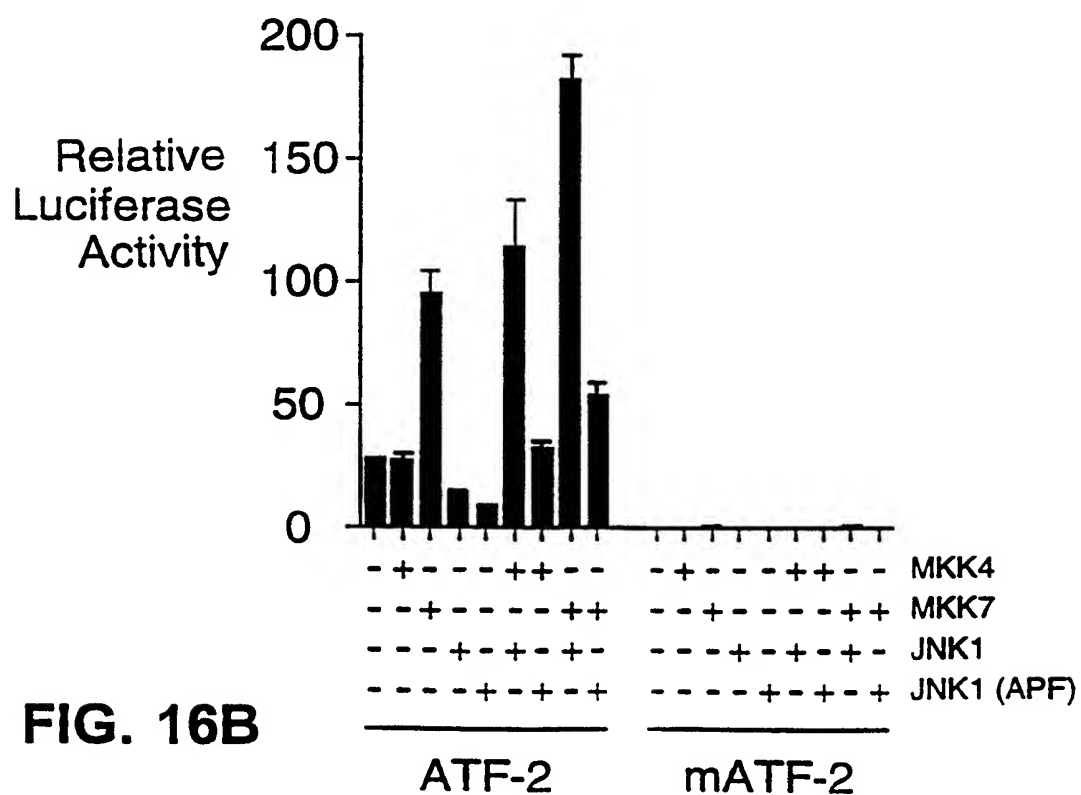
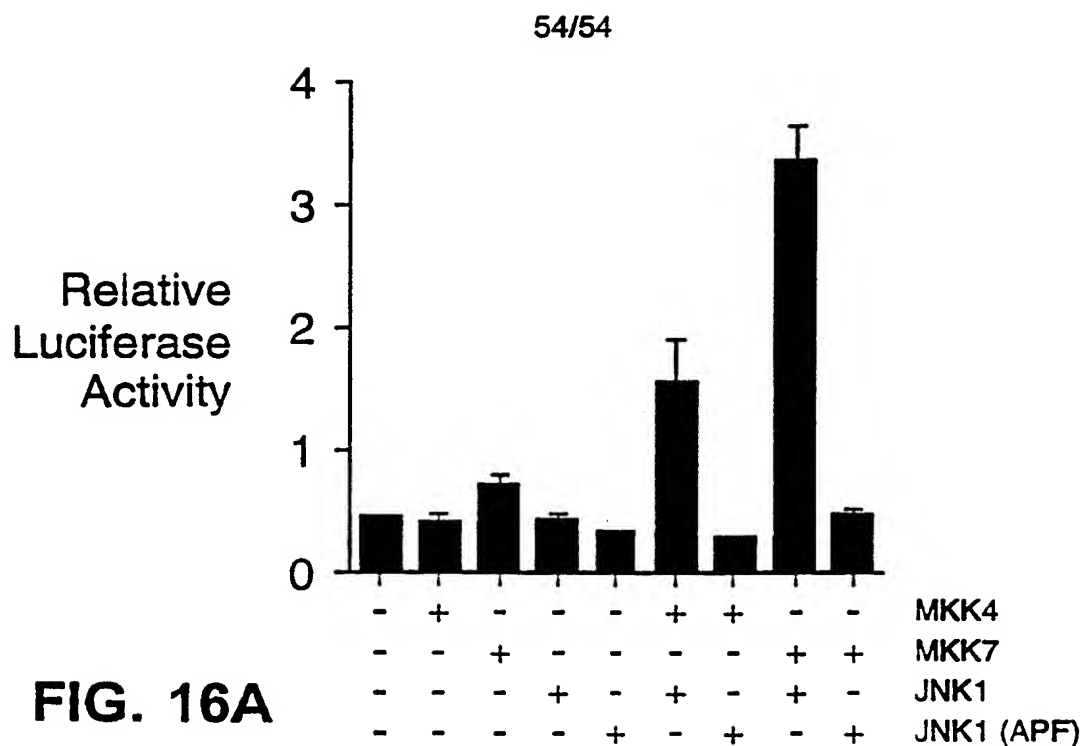
      1470      1480      1490      1500      1510      1520
      *      *      *      *      *      *
GTCCCACCCT CTGACCTCCT CCTCAGGCCA CCAGTGTTCG CCTCTTCCCT TTTTAAACA
CAGGGTGGGA GACTGGAGGA GGAGTCCGGT GGTCAACAACG GGAGAAGGGA AAAATTTTGT

      1530      1540      1550      1560      1570      1580
      *      *      *      *      *      *
AAATACCCTT GTTTGTAAAT CCTTAGACGC TTGAGAATAA AACCCTTCCC TTTCTTCCG
TTTATGGGAA CAAACATTTA GGAATCTGCG AACTCTTATT TTGGGAAGGG AAAAGAAGGC

      1590
      *      *
AAAAAAAAAA AAAAAAAAA (SEQ ID NO: 31)
TTTTTTTTTT TTTTTTTT

```

FIG. 15D



SEQUENCE LISTING

5 (1) GENERAL INFORMATION

(i) APPLICANT: University of Massachusetts

(ii) TITLE OF THE INVENTION: CYTOKINE-, STRESS-, AND ONCOPROTEIN-
ACTIVATED HUMAN PROTEIN KINASE KINASES

(iii) NUMBER OF SEQUENCES: 34

10 (iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Fish & Richardson P.C.

(B) STREET: 225 Franklin Street

(C) CITY: Boston

15 (D) STATE: MA

(E) COUNTRY: USA

(F) ZIP: 02110-2804

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette

20 (B) COMPUTER: IBM Compatible

(C) OPERATING SYSTEM: Windows95

(D) SOFTWARE: FastSEQ for Windows Version 2.0

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: PCT/US98/14101

(B) FILING DATE: 07-JUL-1998

25 (vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 08/888,429

(B) FILING DATE: 07-JUL-1997

(viii) ATTORNEY/AGENT INFORMATION:

30 (A) NAME: Fasse, Peter J.

(B) REGISTRATION NUMBER: 32,983

(C) REFERENCE/DOCKET NUMBER: 07917/053WO1

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617/542-5070

35 (B) TELEFAX: 617/542-8906

(C) TELEX: 299354

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2030 base pairs

40 (B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

45 (A) NAME/KEY: Coding Sequence

(B) LOCATION: 338...1291

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TGGCTGGCAA	TGGCCTTGCT	GACCTCGAGC	CGGGCCACG	TGGGGACCTT	TGGAGCACAG	60
CCTACGATCC	TGGTGCAAGG	CCGGTGGATG	CAGAGGCCAG	TCCATATACC	ACCCAGGCCT	120
GCGAGGAGCG	TGGTCCCCAC	CCATCCAGCC	CATATGTGCA	AGTGCCCTTG	ACAGAGAGGC	180
50 TGGTCATATC	CATGGTGACC	ATTTATGGGC	CACAACAGGT	CCCCATCTGC	GCAGTGAACC	240

	CTGTGCTGAG CACCTTGCAG ACGTGATCTT GCTTCGTCCT GCAGCACTGT GCGGGGCAGG	300
	AAAATCCAAG AGGAAGAAGG ATCTACGGAT ATCCTGC ATG TCC AAG CCA CCC GCA	355
	Met Ser Lys Pro Pro Ala	
	1 5	
5	CCC AAC CCC ACA CCC CCC CGG AAC CTG GAC TCC CGG ACC TTC ATC ACC	403
	Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp Ser Arg Thr Phe Ile Thr	
	10 15 20	
10	ATT GGA GAC AGA AAC TTT GAG GTG GAG GCT GAT GAC TTG GTG ACC ATC	451
	Ile Gly Asp Arg Asn Phe Glu Val Glu Ala Asp Asp Leu Val Thr Ile	
	25 30 35	
	TCA GAA CTG GGC CGT GGA GCC TAT GGG GTG GTA GAG AAG GTG CGG CAC	499
	Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val Val Glu Lys Val Arg His	
	40 45 50	
15	GCC CAG AGC GGC ACC ATC ATG GCC GTG AAG CGG ATC CGG GCC ACC GTG	547
	Ala Gln Ser Gly Thr Ile Met Ala Val Lys Arg Ile Arg Ala Thr Val	
	55 60 65 70	
	AAC TCA CAG GAG CAG AAG CGG CTG CTC ATG GAC CTG GAC ATC AAC ATG	595
	Asn Ser Gln Glu Gln Lys Arg Leu Leu Met Asp Leu Asp Ile Asn Met	
	75 80 85	
20	CGC ACG GTC GAC TGT TTC TAC ACT GTC ACC TTC TAC GGG GCA CTA TTC	643
	Arg Thr Val Asp Cys Phe Tyr Thr Val Thr Phe Tyr Gly Ala Leu Phe	
	90 95 100	
25	AGA GAG GGA GAC GTG TGG ATC TGC ATG GAG CTC ATG GAC ACA TCC TTG	691
	Arg Glu Gly Asp Val Trp Ile Cys Met Glu Leu Met Asp Thr Ser Leu	
	105 110 115	
	GAC AAG TTC TAC CGG AAG GTG CTG GAT AAA AAC ATG ACA ATT CCA GAG	739
	Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys Asn Met Thr Ile Pro Glu	
	120 125 130	
30	GAC ATC CTT GGG GAG ATT GCT GTG TCT ATC GTG CGG GCC CTG GAG CAT	787
	Asp Ile Leu Gly Glu Ile Ala Val Ser Ile Val Arg Ala Leu Glu His	
	135 140 145 150	
35	CTG CAC AGC AAG CTG TCG GTG ATC CAC AGA GAT GTG AAG CCC TCC AAT	835
	Leu His Ser Lys Leu Ser Val Ile His Arg Asp Val Lys Pro Ser Asn	
	155 160 165	
	GTC CTT ATC AAC AAG GAG GGC CAT GTG AAG ATG TGT GAC TTT GGC ATC	883
	Val Leu Ile Asn Lys Glu Gly His Val Lys Met Cys Asp Phe Gly Ile	
	170 175 180	
40	AGT GGC TAC TTG GTG GAC TCT GTG GCC AAG ACG ATG GAT GCC GGC TGC	931
	Ser Gly Tyr Leu Val Asp Ser Val Ala Lys Thr Met Asp Ala Gly Cys	
	185 190 195	
	AAG CCC TAC ATG GCC CCT GAG AGG ATC AAC CCA GAG CTG AAC CAG AAG	979
	Lys Pro Tyr Met Ala Pro Glu Arg Ile Asn Pro Glu Leu Asn Gln Lys	
	200 205 210	
45	GGC TAC AAT GTC AAG TCC GAC GTC TGG AGC CTG GGC ATC ACC ATG ATT	1027
	Gly Tyr Asn Val Lys Ser Asp Val Trp Ser Leu Gly Ile Thr Met Ile	
	215 220 225 230	
50	GAG ATG GCC ATC CTG CGG TTC CCT TAC GAG TCC TGG GGG ACC CCG TTC	1075
	Glu Met Ala Ile Leu Arg Phe Pro Tyr Glu Ser Trp Gly Thr Pro Phe	
	235 240 245	

	CAG CAG CTG AAG CAG GTG GTG GAG GAG CCG TCC CCC CAG CTC CCA GCC	1123
	Gln Gln Leu Lys Gln Val Val Glu Glu Pro Ser Pro Gln Leu Pro Ala	
	250 255 260	
5	GAC CGT TTC TCC CCC GAG TTT GTG GAC TTC ACT GCT CAG TGC CTG AGG	1171
	Asp Arg Phe Ser Pro Glu Phe Val Asp Phe Thr Ala Gln Cys Leu Arg	
	265 270 275	
	AAG AAC CCC GCA GAG CGT ATG AGC TAC CTG GAG CTG ATG GAG CAC CCC	1219
	Lys Asn Pro Ala Glu Arg Met Ser Tyr Leu Glu Leu Met Glu His Pro	
	280 285 290	
10	TTC TTC ACC TTG CAC AAA ACC AAG AAG ACG GAC ATT GCT GCC TTC GTG	1267
	Phe Phe Thr Leu His Lys Thr Lys Lys Thr Asp Ile Ala Ala Phe Val	
	295 300 305 310	
15	AAG AAG ATC CTG GGA GAA GAC TCA TAGGGGCTGG GCCTCGGACC CCACTCCGGC	1321
	Lys Lys Ile Leu Gly Glu Asp Ser	
	315	
	CCTCCAGAGC CCCACAGCCC CATCTGCGGG GGCAGTGCTC ACCCACACCA TAAGCTACTG	1381
	CCATCCTGGC CCAGGGCATC TGGGAGGAAC CGAGGGGGCT GCTCCACCT GGCTCTGTGG	1441
	CGAGCCATTT GTCCCAAGTG CCAAAGAAGC AGACCATTTG GGCTCCAGC CAGGCCCTTG	1501
20	TCGGCCCCAC CAGTGCCTCT CCCTGCTGCT CCTAGGACCC GTCTCCAGCT GCTGAGATCC	1561
	TGGACTGAGG GGGCCTGGAT GCCCCCTGTG GATGCTGCTG CCCCTGCACA GCAGGCTGCC	1621
	AGTGCCTGGG TGGATGGGCC ACCGCCTTGC CCAGCCTGGA TGCCATCCAA GTTGTATATT	1681
	TTTTTAATCT CTCGACTGAA TGGACTTTGC ACACCTTTGGC CCAGGGTGGC CACACCTCTA	1741
	TCCCGGCTTT GGTGCGGGGT ACACAAGAGG GGATGAGTTG TGTGAATACC CCAAGACTCC	1801
	CATGAGGGAG ATGCCATGAG CCGCCCAAGG CCTTCCCCTG GCACTGGCAA ACAGGGCCTC	1861
25	TGCGGAGCAC ACTGGCTCAC CCAGTCCTGC CCGCCACCGT TATCGGTGTC ATTCACCTTT	1921
	CGTGTTTTTT TTAATTTATC CTCTGTTGAT TTTTCTTTT GCTTTATGGG TTTGGCTTGT	1981
	TTTTCTTGCA TGGTTTGGAG CTGATCGCTT CTCCCCCACC CCCTAGGGG	2030

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 318 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

	Met Ser Lys Pro Pro Ala Pro Asn Pro Thr Pro Pro Arg Asn Leu Asp	
	1 5 10 15	
	Ser Arg Thr Phe Ile Thr Ile Gly Asp Arg Asn Phe Glu Val Glu Ala	
	20 25 30	
40	Asp Asp Leu Val Thr Ile Ser Glu Leu Gly Arg Gly Ala Tyr Gly Val	
	35 40 45	
	Val Glu Lys Val Arg His Ala Gln Ser Gly Thr Ile Met Ala Val Lys	
	50 55 60	
45	Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu Leu Met	
	65 70 75 80	
	Asp Leu Asp Ile Asn Met Arg Thr Val Asp Cys Phe Tyr Thr Val Thr	
	85 90 95	
	Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys Met Glu	
	100 105 110	
50	Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Arg Lys Val Leu Asp Lys	
	115 120 125	
	Asn Met Thr Ile Pro Glu Asp Ile Leu Gly Glu Ile Ala Val Ser Ile	
	130 135 140	

4

	Val	Arg	Ala	Leu	Glu	His	Leu	His	Ser	Lys	Leu	Ser	Val	Ile	His	Arg
	145					150					155					160
	Asp	Val	Lys	Pro	Ser	Asn	Val	Leu	Ile	Asn	Lys	Glu	Gly	His	Val	Lys
					165					170					175	
5	Met	Cys	Asp	Phe	Gly	Ile	Ser	Gly	Tyr	Leu	Val	Asp	Ser	Val	Ala	Lys
				180					185					190		
	Thr	Met	Asp	Ala	Gly	Cys	Lys	Pro	Tyr	Met	Ala	Pro	Glu	Arg	Ile	Asn
			195					200					205			
10	Pro	Glu	Leu	Asn	Gln	Lys	Gly	Tyr	Asn	Val	Lys	Ser	Asp	Val	Trp	Ser
		210				215						220				
	Leu	Gly	Ile	Thr	Met	Ile	Glu	Met	Ala	Ile	Leu	Arg	Phe	Pro	Tyr	Glu
	225					230					235					240
	Ser	Trp	Gly	Thr	Pro	Phe	Gln	Gln	Leu	Lys	Gln	Val	Val	Glu	Glu	Pro
					245					250					255	
15	Ser	Pro	Gln	Leu	Pro	Ala	Asp	Arg	Phe	Ser	Pro	Glu	Phe	Val	Asp	Phe
				260					265						270	
	Thr	Ala	Gln	Cys	Leu	Arg	Lys	Asn	Pro	Ala	Glu	Arg	Met	Ser	Tyr	Leu
			275					280					285			
20	Glu	Leu	Met	Glu	His	Pro	Phe	Thr	Leu	His	Lys	Thr	Lys	Lys	Thr	
		290				295					300					
	Asp	Ile	Ala	Ala	Phe	Val	Lys	Lys	Ile	Leu	Gly	Glu	Asp	Ser		
	305					310					315					

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1602 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 244...1245

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

35	TAGCTGCAGC	ACAGCCTTCC	CTAACGTTGC	AACTGGGGGA	AAAATCACTT	TCCAGTCTGT	60
	TTTGCAAGGT	GTGCATTTC	ATCTTGATTC	CCTGAAAGTC	CATCTGCTGC	ATCGGTCAAG	120
	AGAAACTCCA	CTTGCATGAA	GATTGCACGC	CTGCAGCTTG	CATCTTTGTT	GCAAAACTAG	180
	CTACAGAAGA	GAAGCAAGGC	AAAGTCTTTT	GTGCTCCCCT	CCCCCATCAA	AGGAAAGGGG	240
	AAA ATG TCT CAG TCG AAA GGC AAG AAG CGA AAC	CCT GGC CTT AAA ATT	288				
40	Met Ser Gln Ser Lys Gly Lys Lys Arg Asn Pro Gly Leu Lys Ile	1 5 10 15					
	CCA AAA GAA GCA TTT GAA CAA CCT CAG ACC AGT TCC ACA CCA CCT AGA	336					
	Pro Lys Glu Ala Phe Glu Gln Pro Gln Thr Ser Ser Thr Pro Pro Arg	20 25 30					
45	GAT TTA GAC TCC AAG GCT TGC ATT TCT ATT GGA AAT CAG AAC TTT GAG	384					
	Asp Leu Asp Ser Lys Ala Cys Ile Ser Ile Gly Asn Gln Asn Phe Glu	35 40 45					
	GTG AAG GCA GAT GAC CTG GAG CCT ATA ATG GAA CTG GGA CGA GGT GCG	432					
	Val Lys Ala Asp Asp Leu Glu Pro Ile Met Glu Leu Gly Arg Gly Ala	50 55 60					
50	TAC GGG GTG GTG GAG AAG ATG CGG CAC GTG CCC AGC GGG CAG ATC ATG	480					
	Tyr Gly Val Val Glu Lys Met Arg His Val Pro Ser Gly Gln Ile Met	65 70 75					

5

	GCA GTG AAG CGG ATC CGA GCC ACA GTA AAT AGC CAG GAA CAG AAA CGG Ala Val Lys Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg 80 85 90 95	528
5	CTA CTG ATG GAT TTG GAT ATT TCC ATG AGG ACG GTG GAC TGT CCA TTC Leu Leu Met Asp Leu Asp Ile Ser Met Arg Thr Val Asp Cys Pro Phe 100 105 110	576
	ACT GTC ACC TTT TAT GGC GCA CTG TTT CGG GAG GGT GAT GTG TGG ATC Thr Val Thr Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile 115 120 125	624
10	TGC ATG GAG CTC ATG GAT ACA TCA CTA GAT AAA TTC TAC AAA CAA GTT Cys Met Glu Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Lys Gln Val 130 135 140	672
15	ATT GAT AAA GGC CAG ACA ATT CCA GAG GAC ATC TTA GGG AAA ATA GCA Ile Asp Lys Gly Gln Thr Ile Pro Glu Asp Ile Leu Gly Lys Ile Ala 145 150 155	720
	GTT TCT ATT GTA AAA GCA TTA GAA CAT TTA CAT AGT AAG CTG TCT GTC Val Ser Ile Val Lys Ala Leu Glu His Leu His Ser Lys Leu Ser Val 160 165 170 175	768
20	ATT CAC AGA GAC GTC AAG CCT TCT AAT GTA CTC ATC AAT GCT CTC GGT Ile His Arg Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly 180 185 190	816
	CAA GTG AAG ATG TGC GAT TTT GGA ATC AGT GGC TAC TTG GTG GAC TCT Gln Val Lys Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser 195 200 205	864
25	GTT GCT AAA ACA ATT GAT GCA GGT TGC AAA CCA TAC ATG GCC CCT GAA Val Ala Lys Thr Ile Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu 210 215 220	912
30	AGA ATA AAC CCA GAG CTC AAC CAG AAG GGA TAC AGT GTG AAG TCT GAC Arg Ile Asn Pro Glu Leu Asn Gln Lys Gly Tyr Ser Val Lys Ser Asp 225 230 235	960
	ATT TGG AGT CTG GGC ATC ACG ATG ATT GAG TTG GCC ATC CTT CGA TTT Ile Trp Ser Leu Gly Ile Thr Met Ile Glu Leu Ala Ile Leu Arg Phe 240 245 250 255	1008
35	CCC TAT GAT TCA TGG GGA ACT CCA TTT CAG CAG CTC AAA CAG GTG GTA Pro Tyr Asp Ser Trp Gly Thr Pro Phe Gln Gln Leu Lys Gln Val Val 260 265 270	1056
	GAG GAG CCA TCG CCA CAA CTC CCA GCA GAC AAG TTC TCT GCA GAG TTT Glu Glu Pro Ser Pro Gln Leu Pro Ala Asp Lys Phe Ser Ala Glu Phe 275 280 285	1104
40	GTT GAC TTT ACC TCA CAG TGC TTA AAG AAG AAT TCC AAA GAA CGG CCT Val Asp Phe Thr Ser Gln Cys Leu Lys Lys Asn Ser Lys Glu Arg Pro 290 295 300	1152
45	ACA TAC CCA GAG CTA ATG CAA CAT CCA TTT TTC ACC CTA CAT GAA TCC Thr Tyr Pro Glu Leu Met Gln His Pro Phe Phe Thr Leu His Glu Ser 305 310 315	1200
	AAA GGA ACA GAT GTG GCA TCT TTT GTA AAA CTG ATT CTT GGA GAC TAAAA Lys Gly Thr Asp Val Ala Ser Phe Val Lys Leu Ile Leu Gly Asp 320 325 330	1250
50	AGCAGTGGAC TTAATCGGTT GACCCTACTG TGGATTGGTG GGTTTCGGGG TGAAGCAAGT TCACTACAGC ATCAATAGAA AGTCATCTTT GAGATAATTT AACCCCTGCCT CTCAGAGGGT TTTCTCTCCC AATTTTCTTT TTAATCCCCC TCTTAAGGGG GCCTTGGAAT CTATAGTATA 1310 1370 1430	

```

GAATGAACTG TCTAGATGGA TGAATTATGA TAAAGGCTTA GGACTTCAAA AGGTGATTAA 1490
ATATTTAATG ATGTGTCATA TGAGTCCTCA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1550
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AA 1602

```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 334 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Met Ser Gln Ser Lys Gly Lys Lys Arg Asn Pro Gly Leu Lys Ile Pro
  1      5      10      15
Lys Glu Ala Phe Glu Gln Pro Gln Thr Ser Ser Thr Pro Pro Arg Asp
  20      25      30
Leu Asp Ser Lys Ala Cys Ile Ser Ile Gly Asn Gln Asn Phe Glu Val
  35      40      45
Lys Ala Asp Asp Leu Glu Pro Ile Met Glu Leu Gly Arg Gly Ala Tyr
  50      55      60
Gly Val Val Glu Lys Met Arg His Val Pro Ser Gly Gln Ile Met Ala
  65      70      75      80
Val Lys Arg Ile Arg Ala Thr Val Asn Ser Gln Glu Gln Lys Arg Leu
  85      90      95
Leu Met Asp Leu Asp Ile Ser Met Arg Thr Val Asp Cys Pro Phe Thr
 100      105      110
Val Thr Phe Tyr Gly Ala Leu Phe Arg Glu Gly Asp Val Trp Ile Cys
 115      120      125
Met Glu Leu Met Asp Thr Ser Leu Asp Lys Phe Tyr Lys Gln Val Ile
 130      135      140
Asp Lys Gly Gln Thr Ile Pro Glu Asp Ile Leu Gly Lys Ile Ala Val
 145      150      155      160
Ser Ile Val Lys Ala Leu Glu His Leu His Ser Lys Leu Ser Val Ile
 165      170      175
His Arg Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly Gln
 180      185      190
Val Lys Met Cys Asp Phe Gly Ile Ser Gly Tyr Leu Val Asp Ser Val
 195      200      205
Ala Lys Thr Ile Asp Ala Gly Cys Lys Pro Tyr Met Ala Pro Glu Arg
 210      215      220
Ile Asn Pro Glu Leu Asn Gln Lys Gly Tyr Ser Val Lys Ser Asp Ile
 225      230      235      240
Trp Ser Leu Gly Ile Thr Met Ile Glu Leu Ala Ile Leu Arg Phe Pro
 245      250      255
Tyr Asp Ser Trp Gly Thr Pro Phe Gln Leu Lys Gln Val Val Glu
 260      265      270
Glu Pro Ser Pro Gln Leu Pro Ala Asp Lys Phe Ser Ala Glu Phe Val
 275      280      285
Asp Phe Thr Ser Gln Cys Leu Lys Lys Asn Ser Lys Glu Arg Pro Thr
 290      295      300
Tyr Pro Glu Leu Met Gln His Pro Phe Phe Thr Leu His Glu Ser Lys
 305      310      315      320
Gly Thr Asp Val Ala Ser Phe Val Lys Leu Ile Leu Gly Asp
 325      330

```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3498 base pairs

(B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

5

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 40...1128

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

10	CTAGGGTCCC CGGCGCCAGG CCACCCGGCC GTCAGCAGC ATG CAG GGT AAA CGC	54
	Met Gln Gly Lys Arg	
	1 5	
	AAA GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC AAA TCT ACA GCA	102
	Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Phe Lys Ser Thr Ala	
	10 15 20	
15	AGG TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA AAC CCA CAC ATA	150
	Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln Asn Pro His Ile	
	25 30 35	
	GAG AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA AAA CTG AAG ATC	198
	Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly Lys Leu Lys Ile	
20	40 45 50	
	TCC CCT GAA CAA CAC TGG GAT TTC ACT GCA GAG GAC TTG AAA GAC CTT	246
	Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp Leu Lys Asp Leu	
	55 60 65	
	GGA GAA ATT GGA CGA GGA GCT TAT GGT TCT GTC AAC AAA ATG GTC CAC	294
25	Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn Lys Met Val His	
	70 75 80 85	
	AAA CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT CGG TCA ACA GTG	342
	Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile Arg Ser Thr Val	
	90 95 100	
30	GAT GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG GAT GTA GTA ATG	390
	Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu Asp Val Val Met	
	105 110 115	
35	CGG AGT AGT GAT TGC CCA TAC ATT GTT CAG TTT TAT GGT GCA CTC TTC	438
	Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr Gly Ala Leu Phe	
	120 125 130	
	AGA GAG GGT GAC TGT TGG ATC TGT ATG GAA CTC ATG TCT ACC TCG TTT	486
	Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met Ser Thr Ser Phe	
	135 140 145	
40	GAT AAG TTT TAC AAA TAT GTA TAT AGT GTA TTA GAT GAT GTT ATT CCA	534
	Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp Asp Val Ile Pro	
	150 155 160 165	
	GAA GAA ATT TTA GGC AAA ATC ACT TTA GCA ACT GTG AAA GCA CTA AAC	582
	Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val Lys Ala Leu Asn	
45	170 175 180	
	CAC TTA AAA GAA AAC TTG AAA ATT ATT CAC AGA GAT ATC AAA CCT TCC	630
	His Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp Ile Lys Pro Ser	
	185 190 195	

	AAT ATT CTT CTG GAC AGA AGT GGA AAT ATT AAG CTC TGT GAC TTC GGC	678
	Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu Cys Asp Phe Gly	
	200 205 210	
5	ATC AGT GGA CAG CTT GTG GAC TCT ATT GCC AAG ACA AGA GAT GCT GGC	726
	Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr Arg Asp Ala Gly	
	215 220 225	
	TGT AGG CCA TAC ATG GCA CCT GAA AGA ATA GAC CCA AGC GCA TCA CGA	774
	Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro Ser Ala Ser Arg	
	230 235 240 245	
10	CAA GGA TAT GAT GTC CGC TCT GAT GTC TGG AGT TTG GGG ATC ACA TTG	822
	Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu Gly Ile Thr Leu	
	250 255 260	
15	TAT GAG TTG GCC ACA GGC CGA TTT CCT TAT CCA AAG TGG AAT AGT GTA	870
	Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys Trp Asn Ser Val	
	265 270 275	
	TTT GAT CAA CTA ACA CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT	918
	Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser	
	280 285 290	
20	AAT TCT GAG GAA AGG GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC	966
	Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Asn	
	295 300 305	
	TTG TGC CTT ACG AAG GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT	1014
	Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu	
	310 315 320 325	
25	CTG AAA CAT CCC TTT ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC	1062
	Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val	
	330 335 340	
30	GCA TGC TAT GTT TGT AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC	1110
	Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser	
	345 350 355	
	TCT CCC ATG TAT GTC GAT TGATATCGYT GCTACATCAG ACTCTAGAAA AAAGGGCT	1166
	Ser Pro Met Tyr Val Asp	
	360	
35	GAGAGGAAAGC AAGACGTAAA GAATTTTCAT CCCGTATCAC AGTGTTTTTA TTGCTCGCCC	1226
	AGACACCATG TGCAATAAGA TTGGTGTTTCG TTTCCATCAT GTCTGTATAC TCCTGTCACC	1286
	TAGAACGTGC ATCCTTGTA TACCTGATTG ATCACACAGT GTTAGTGCTG GTCAGAGAGA	1346
	CCTCATCCTG CTCTTTTGTG ATGAACATAT TCATGAAATG TGGAAGTCAG TACGATCAAG	1406
	TTGTTGACTG TGATTAGATC ACATCTTAAA TTCATTCTA GACTCAAAAC CTGGAGATGC	1466
	AGCTACTGGA ATGGTGTTTT GTCAGACTTC CAAATCCTGG AAGGACACAG TGATGAATGT	1526
40	ACTATATCTG AACATAGAAA CTCGGGCTTG AGTGAGAAGA GCTTGACACAG CCAACGAGAC	1586
	ACATTGCCTT CTGGAGCTGG GAGACAAAGG AGGAATTTAC TTTCTTCACC AAGTGCAATA	1646
	GATTACTGAT GTGATATTCT GTTGCTTTAC AGTTACAGTT GATGTTTGGG GATCGATGTG	1706
	CTCAGCCAAA TTTCCTGTTT GAAATATCAT GTTAAATTAG AATGAATTTA TCTTTACCAA	1766
	AAACCATGTT GCGTTCAAAG AGGTGAACAT TAAAATATAG AGACAGGACA GAATGTGTTC	1826
45	TTTTCTCCTC TACCACTCCT ATTTTTCAT GGGAAAGACTC AGGAGTCTGC CACTTGTCAA	1886
	AGAAGGTGCT GATCCTAAGA ATTTTTCATT CTCAGAATTC GGTGTGCTGC CAACTTGATG	1946
	TTCCACCTGC CACAAACCAC CAGGACTGAA AGAAGAAAAC AGTACAGAAG GCAAAGTTTA	2006
	CAGATGTTTT TAATTCTAGT ATTTTATCTG GAACAACCTG TAGCAGCTAT ATATTTCCCC	2066
	TTGGTCCCAA GCCTGATACT TTAGCCATCA TAACTCACTA ACAGGGAGAA GTAGCTAGTA	2126
50	GCAATGTGCC TTGATTGATT AGATAAAGAT TTCTAGTAGG CAGCAAAAGA CCAAATCTCA	2186
	GTGTTTGTCT TCTTGCCATC ACTGGTCCAG GTCTTCAGTT TCCGAATCTC TTTCCCTTCC	2246
	CCTGTGGTCT ATTGTCGCTA TGTGACTTGC GCTTAATCCA ATATTTTGCC TTTTTCCTAT	2306
	ATCAAAAAAC CTTTACAGTT AGCAGGGATG TTCCTTACCG AGGATTTTTA ACCCCCAATC	2366
	TCTCATAATC GCTAGTGTTC AAAAGGCTAA GAATAGTGGG GCCCAACCGA TGTGGTAGGT	2426
55	GATAAAGAGG CATCTTTTCT AGAGACACAT TGGACCAGAT GAGGATCCGA AACGGCAGCC	2486
	TTTACGTTCA TCACCTGCTA GAACCTCTCG TAGTCCATCA CCATTTCTTG GCATTGGAAT	2546

	TCTACTGGAA	AAAAATACAA	AAAGCAAAAC	AAAACCCTCA	GCACTGTTAC	AAGAGGCCAT	2606
	TTAAGTATCT	TGTGCTTCTT	CACTTACCCA	TTAGCCAGGT	TCTCATTAGG	TTTTGCTTGG	2666
	GCCTCCCTGG	CACTGAACCT	TAGGCTTTGT	ATGACAGTGA	AGCAGCACTG	TGAGTGGTTC	2726
5	AAGCACACTG	GAATATAAAA	CAGTCATGGC	CTGAGATGCA	GGTGATGCCA	TTACAGAACC	2786
	AAATCGTGGC	ACGTATTGCT	GTGTCTCCTC	TCAGAGTGAC	AGTCATAAAT	ACTGTCAAAC	2846
	AATAAAGGGA	GAATGGTGCT	GTTTAAAGTC	ACATCCCTGT	AAATTGCAGA	ATTCAAAAGT	2906
	GATTATCTCT	TTGATCTACT	TGCCTCATTT	CCCTATCTTC	TCCCCCACGG	TATCCTAAAC	2966
	TTTAGACTTC	CCACTGTTCT	GAAAGGAGAC	ATTGCTCTAT	GTCTGCCTTC	GACCACAGCA	3026
10	AGCCATCATC	CTCCATTGCT	CCCGGGGACT	CAAGAGGAAT	CTGTTTCTCT	GCTGTCAACT	3086
	TCCCATCTGG	CTCAGCATAG	GGTCACTTTG	CCATTATGCA	AATGGAGATA	AAAGCAATTC	3146
	TGGCTGTCCA	GGAGCTAATC	TGACCGTTCT	ATTGTGTGGA	TGACCACATA	AGAAGGCAAT	3206
	TTTAGTGTAT	TAATCATAGA	TTATTATAAA	CTATAAACTT	AAGGGCAAGG	AGTTTATTAC	3266
	AATGTATCTT	TATTAATAACA	AAAGGGTGTA	TAGTGTTCAC	AAACTGTGAA	AATAGTGTAA	3326
15	GAACGTGTACA	TTGTGAGCTC	TGGTTATTTT	TCTCTTGTA	CATAGAAAAA	TGTATAAAAA	3386
	TTATCAAAAA	GCTAATGTGC	AGGGATATTG	CCTTATTTGT	CTGTAAAAAA	TGGAGCTCAG	3446
	TAACATAACT	GCTTCTTGGA	GCTTTGGAAT	ATTTTATCCT	GTATTCTTGT	TT	3498

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 363 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

25	Met	Gln	Gly	Lys	Arg	Lys	Ala	Leu	Lys	Leu	Asn	Phe	Ala	Asn	Pro	Pro
	1				5					10					15	
	Phe	Lys	Ser	Thr	Ala	Arg	Phe	Thr	Leu	Asn	Pro	Asn	Pro	Thr	Gly	Val
				20					25					30		
30	Gln	Asn	Pro	His	Ile	Glu	Arg	Leu	Arg	Thr	His	Ser	Ile	Glu	Ser	Ser
		35						40					45			
	Gly	Lys	Leu	Lys	Ile	Ser	Pro	Glu	Gln	His	Trp	Asp	Phe	Thr	Ala	Glu
		50					55					60				
	Asp	Leu	Lys	Asp	Leu	Gly	Glu	Ile	Gly	Arg	Gly	Ala	Tyr	Gly	Ser	Val
		65				70				75					80	
35	Asn	Lys	Met	Val	His	Lys	Pro	Ser	Gly	Gln	Ile	Met	Ala	Val	Lys	Arg
				85					90						95	
	Ile	Arg	Ser	Thr	Val	Asp	Glu	Lys	Glu	Gln	Lys	Gln	Leu	Leu	Met	Asp
				100					105					110		
40	Leu	Asp	Val	Val	Met	Arg	Ser	Ser	Asp	Cys	Pro	Tyr	Ile	Val	Gln	Phe
		115						120					125			
	Tyr	Gly	Ala	Leu	Phe	Arg	Glu	Gly	Asp	Cys	Trp	Ile	Cys	Met	Glu	Leu
		130					135					140				
	Met	Ser	Thr	Ser	Phe	Asp	Lys	Phe	Tyr	Lys	Tyr	Val	Tyr	Ser	Val	Leu
		145				150				155					160	
45	Asp	Asp	Val	Ile	Pro	Glu	Glu	Ile	Leu	Gly	Lys	Ile	Thr	Leu	Ala	Thr
				165					170						175	
	Val	Lys	Ala	Leu	Asn	His	Leu	Lys	Glu	Asn	Leu	Lys	Ile	Ile	His	Arg
				180					185					190		
	Asp	Ile	Lys	Pro	Ser	Asn	Ile	Leu	Leu	Asp	Arg	Ser	Gly	Asn	Ile	Lys
50			195					200					205			
	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	Gln	Leu	Val	Asp	Ser	Ile	Ala	Lys
		210					215					220				
	Thr	Arg	Asp	Ala	Gly	Cys	Arg	Pro	Tyr	Met	Ala	Pro	Glu	Arg	Ile	Asp
		225				230				235					240	
55	Pro	Ser	Ala	Ser	Arg	Gln	Gly	Tyr	Asp	Val	Arg	Ser	Asp	Val	Trp	Ser
				245					250						255	
	Leu	Gly	Ile	Thr	Leu	Tyr	Glu	Leu	Ala	Thr	Gly	Arg	Phe	Pro	Tyr	Pro
				260				265						270		
60	Lys	Trp	Asn	Ser	Val	Phe	Asp	Gln	Leu	Thr	Gln	Val	Val	Lys	Gly	Asp
			275					280					285			

10

Pro Pro Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe
 290 295 300
 Ile Asn Phe Val Asn Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro
 305 310 315 320
 5 Lys Tyr Lys Glu Leu Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu
 325 330 335
 Arg Ala Val Glu Val Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met
 340 345 350
 10 Pro Ala Thr Pro Ser Ser Pro Met Tyr Val Asp
 355 360

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 3554 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

20 (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 6...1184

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

	CAACA ATG GCG GCT CCG AGC CCG AGC GGT GGC GGC GGC AGC GGC ACC CCC	50
	Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Thr Pro	
	1 5 10 15	
25	GGC CCC GTA GGG TCC CCG GCG CCA GGC CAC CCG GCC GTC AGC AGC ATG	98
	Gly Pro Val Gly Ser Pro Ala Pro Gly His Pro Ala Val Ser Ser Met	
	20 25 30	
30	CAG GGT AAA CGC AAA GCA CTG AAG TTG AAT TTT GCA AAT CCA CCT TTC	146
	Gln Gly Lys Arg Lys Ala Leu Lys Leu Asn Phe Ala Asn Pro Pro Phe	
	35 40 45	
	AAA TCT ACA GCA AGG TTT ACT CTG AAT CCC AAT CCT ACA GGA GTT CAA	194
	Lys Ser Thr Ala Arg Phe Thr Leu Asn Pro Asn Pro Thr Gly Val Gln	
	50 55 60	
35	AAC CCA CAC ATA GAG AGA CTG AGA ACA CAC AGC ATT GAG TCA TCA GGA	242
	Asn Pro His Ile Glu Arg Leu Arg Thr His Ser Ile Glu Ser Ser Gly	
	65 70 75	
40	AAA CTG AAG ATC TCC CCT GAA CAA CAC TGG GAT TTC ACT GCA GAG GAC	290
	Lys Leu Lys Ile Ser Pro Glu Gln His Trp Asp Phe Thr Ala Glu Asp	
	80 85 90 95	
	TTG AAA GAC CTT GGA GAA ATT GGA CGA GGA GCT TAT GGT TCT GTC AAC	338
	Leu Lys Asp Leu Gly Glu Ile Gly Arg Gly Ala Tyr Gly Ser Val Asn	
	100 105 110	
45	AAA ATG GTC CAC AAA CCA AGT GGG CAA ATA ATG GCA GTT AAA AGA ATT	386
	Lys Met Val His Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile	
	115 120 125	
50	CGG TCA ACA GTG GAT GAA AAA GAA CAA AAA CAA CTT CTT ATG GAT TTG	434
	Arg Ser Thr Val Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu	
	130 135 140	

		GAT Asp	GTA Val	ATA Val	ATG Met	CGG Arg	AGT Ser	AGT Ser	GAT Asp	TGC Cys	CCA Pro	TAC Tyr	ATT Ile	GTT Val	CAG Gln	TTT Phe	TAT Tyr	482
		145						150					155					
5		GGT Gly	GCA Ala	CTC Leu	TTC Phe	AGA Arg	GAG Glu	GGT Gly	GAC Asp	TGT Cys	TGG Trp	ATC Ile	TGT Cys	ATG Met	GAA Glu	CTC Leu	ATG Met	530
		160					165					170					175	
		TCT Ser	ACC Thr	TCG Ser	TTT Phe	GAT Asp	AAG Lys	TTT Phe	TAC Tyr	AAA Lys	TAT Tyr	GTA Val	TAT Tyr	AGT Ser	GTA Val	TTA Leu	GAT Asp	578
		180									185					190		
10		GAT Asp	GTT Val	ATT Ile	CCA Pro	GAA Glu	GAA Glu	ATT Ile	TTA Leu	GGC Gly	AAA Lys	ATC Ile	ACT Thr	TTA Leu	GCA Ala	ACT Thr	GTG Val	626
		195								200					205			
		AAA Lys	GCA Ala	CTA Leu	AAC Asn	CAC His	TTA Leu	AAA Lys	GAA Glu	AAC Asn	TTG Leu	AAA Lys	ATT Ile	ATT Ile	CAC His	AGA Arg	GAT Asp	674
15		210							215					220				
		ATC Ile	AAA Lys	CCT Pro	TCC Ser	AAT Asn	ATT Ile	CTT Leu	CTG Leu	GAC Asp	AGA Arg	AGT Ser	GGA Gly	AAT Asn	ATT Ile	AAG Lys	CTC Leu	722
		225						230					235					
20		TGT Cys	GAC Asp	TTC Phe	GGC Gly	ATC Ile	AGT Ser	GGA Gly	CAG Gln	CTT Leu	GTG Val	GAC Asp	TCT Ser	ATT Ile	GCC Ala	AAG Lys	ACA Thr	770
		240					245					250					255	
		AGA Arg	GAT Asp	GCT Ala	GGC Gly	TGT Cys	AGG Arg	CCA Pro	TAC Tyr	ATG Met	GCA Ala	CCT Pro	GAA Glu	AGA Arg	ATA Ile	GAC Asp	CCA Pro	818
		260				265					265					270		
25		AGC Ser	GCA Ala	TCA Ser	CGA Arg	CAA Gln	GGA Gly	TAT Tyr	GAT Asp	GTC Val	CGC Arg	TCT Ser	GAT Asp	GTC Val	TGG Trp	AGT Ser	TTG Leu	866
		275								280					285			
		GGG Gly	ATC Ile	ACA Thr	TTG Leu	TAT Tyr	GAG Glu	TTG Leu	GCC Ala	ACA Thr	GGC Gly	CGA Arg	TTT Phe	CCT Pro	TAT Tyr	CCA Pro	AAG Lys	914
30		290							295					300				
		TGG Trp	AAT Asn	AGT Ser	GTA Val	TTT Phe	GAT Asp	CAA Gln	CTA Leu	ACA Thr	CAA Gln	GTC Val	GTG Val	AAA Lys	GGA Gly	GAT Asp	CCT Pro	962
		305						310					315					
35		CCG Pro	CAG Gln	CTG Leu	AGT Ser	AAT Asn	TCT Ser	GAG Glu	GAA Glu	AGG Arg	GAA Glu	TTC Phe	TCC Ser	CCG Pro	AGT Ser	TTC Phe	ATC Ile	1010
		320					325					330					335	
		AAC Asn	TTT Phe	GTC Val	AAC Asn	TTG Leu	TGC Cys	CTT Leu	ACG Thr	AAG Lys	GAT Asp	GAA Glu	TCC Ser	AAA Lys	AGG Arg	CCA Pro	AAG Lys	1058
		340				345					345					350		
40		TAT Tyr	AAA Lys	GAG Glu	CTT Leu	CTG Leu	AAA Lys	CAT His	CCC Pro	TTT Phe	ATT Ile	TTG Leu	ATG Met	TAT Tyr	GAA Glu	GAA Glu	CGT Arg	1106
		355						360							365			
		GCC Ala	GTT Val	GAG Glu	GTC Val	GCA Ala	TGC Cys	TAT Tyr	GTT Val	TGT Cys	AAA Lys	ATC Ile	CTG Leu	GAT Asp	CAA Gln	ATG Met	CCA Pro	1154

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	TGCTGGTCAG	AGAGACCTCA	TCCTGCTCTT	TTGTGATGAA	CATATTCATG	AAATGTGGAA	1447
	GTCAGTACGA	TCAAGTTGTT	GACTGTGATT	AGATCACATC	TTAAATTCAT	TTCTAGACTC	1507
	AAAACCTGGA	GATGCAGCTA	CTGGAATGGT	GTTTTGTCAG	ACTTCCAAAT	CCTGGAAGGA	1567
5	CACAGTGATG	AATGTACTAT	ATCTGAACAT	AGAAACTCGG	GCTTGAGTGA	GAAGAGCTTG	1627
	CACAGCCAAC	GAGACACATT	GCCTTCTGGA	GCTGGGAGAC	AAAGGAGGAA	TTTACTTTCT	1687
	TCACCAAGTG	CAATAGATTA	CTGATGTGAT	ATTCTGTTGC	TTTACAGTTA	CAGTTGATGT	1747
	TTGGGGATCG	ATGTGCTCAG	CCAAATTTCC	TGTTTGAAAT	ATCATGTTAA	ATTAGAATGA	1807
	ATTTATCTTT	ACCAAAAACC	ATGTTGCGTT	CAAAGAGGTG	AACATTAATA	TATAGAGACA	1867
	GGACAGAATG	TGTTCTTTTC	TCCTCTACCA	GTCTATTTTT	TCAATGGGAA	GACTCAGGAG	1927
10	TCTGCCACTT	GTCAAAGAAG	GTGCTGATCC	TAAGAATTTT	TCATTCTCAG	AATTCCGGTG	1987
	GCTGCCAACT	TGATGTTCCA	CCTGCCACAA	ACCACCAGGA	CTGAAAGAAG	AAAACAGTAC	2047
	AGAAGGCAAA	GTTTACAGAT	GTTTTTAATT	CTAGTATTTT	ATCTGGAACA	ATTTGTAGCA	2107
	GCTATATATT	TCCCCTTGGT	CCCAAGCCTG	ATACTTTAGC	CATCATAACT	CACTAACAGG	2167
	GAGAAGTAGC	TAGTAGCAAT	GTGCCTTGAT	TGATTAGATA	AAGATTTCTA	GTAGGCAGCA	2227
15	AAAGACCAAA	TCTCAGTTGT	TTGCTTCTGT	CCATCACTGG	TCCAGGTCTT	CAGTTTCCGA	2287
	ATCTCTTTCC	CTTCCCCTGT	GGTCTATTGT	CGCTATGTGA	CTTGCGCTTA	ATCCAATATT	2347
	TTGCCTTTTT	TCTATATCAA	AAAACCTTTA	CAGTTAGCAG	GGATGTTTCT	TACCGAGGAT	2407
	TTTTAACCCC	CAATCTCTCA	TAATCGCTAG	TGTTTTAAAG	GCTAAGAATA	GTGGGGCCCCA	2467
	ACCGATGTGG	TAGGTGATAA	AGAGGCATCT	TTTCTAGAGA	CACATTGGAC	CAGATGAGGA	2527
20	TCCGAAACGG	CAGCCTTTAC	GTTTCATCAC	TGCTAGAACC	TCTCGTAGTC	CATCACCATT	2587
	TCTTGGCATT	GGAATTCTAC	TGGAAAAAAA	TACAAAAAGC	AAAACAAAAC	CCTCAGCACT	2647
	GTTACAAGAG	GCCATTTAAG	TATCTTGTGC	TTCTTCACTT	ACCCATTAGC	CAGGTTCTCA	2707
	TTAGGTTTTG	CTTGGGCCTC	CCTGGCACTG	AACCTTAGGC	TTTGTATGAC	AGTGAAGCAG	2767
	CACTGTGAGT	GGTTCAAGCA	CACTGGAATA	TAAAACAGTC	ATGGCCTGAG	ATGCAGGTGA	2827
25	TGCCATTACA	GAACCAAATC	GTGGCACGTA	TTGCTGTGTC	TCCTCTCAGA	GTGACAGTCA	2887
	TAAATACTGT	CAAACAATAA	AGGGAGAATG	GTGCTGTTTA	AAGTCACATC	CCTGTAAATT	2947
	GCAGAATTCA	AAAGTGATTA	TCTCTTTGAT	CTACTTGCCCT	CATTTCCCTA	TCTTCTCCCC	3007
	CACGGTATCC	TAAACTTTAG	ACTTCCCCT	GTTCTGAAAG	GAGACATTGC	TCTATGTCTG	3067
30	CCTTCGACCA	CAGCAAGCCA	TCATCCTCCA	TTGCTCCCGG	GGACTCAAGA	GGAATCTGTT	3127
	TCTCTGCTGT	CAACTTCCCA	TCTGGCTCAG	CATAGGGTCA	CTTTGCCATT	ATGCAAATGG	3187
	AGATAAAAGC	AATTCTGGCT	GTCCAGGAGC	TAATCTGACC	GTTCTATTGT	GTGGATGACC	3247
	ACATAAGAAG	GCAATTTTAG	TGTATTAATC	ATAGATTATT	ATAAACTATA	AACTTAAGGG	3307
	CAAGGAGTTT	ATTACAATGT	ATCTTTATTA	AAACAAAAGG	GTGTATAGTG	TTACACAACT	3367
	GTGAAAATAG	TGTAAGAATG	GTACATTGTG	AGCTCTGGTT	ATTTTTCTCT	TGTACCATAG	3427
35	AAAAATGTAT	AAAAATTATC	AAAAAGCTAA	TGTGCAGGGA	TATTGCCTTA	TTTGTCTGTA	3487
	AAAAATGGAG	CTCAGTAACA	TAAGTCTTTC	TTGGAGCTTT	GGAATATTTT	ATCCTGTATT	3547
	CTTGTTT						3554

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 393 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

	Met	Ala	Ala	Pro	Ser	Pro	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Thr	Pro	Gly
	1				5					10					15	
	Pro	Val	Gly	Ser	Pro	Ala	Pro	Gly	His	Pro	Ala	Val	Ser	Ser	Met	Gln
				20					25					30		
50	Gly	Lys	Arg	Lys	Ala	Leu	Lys	Leu	Asn	Phe	Ala	Asn	Pro	Phe	Lys	
				35				40					45			
	Ser	Thr	Ala	Arg	Phe	Thr	Leu	Asn	Pro	Asn	Pro	Thr	Gly	Val	Gln	Asn
				50			55					60				
	Pro	His	Ile	Glu	Arg	Leu	Arg	Thr	His	Ser	Ile	Glu	Ser	Ser	Gly	Lys
55						70						75			80	
	Leu	Lys	Ile	Ser	Pro	Glu	Gln	His	Trp	Asp	Phe	Thr	Ala	Glu	Asp	Leu
						85				90				95		
	Lys	Asp	Leu	Gly	Glu	Ile	Gly	Arg	Gly	Ala	Tyr	Gly	Ser	Val	Asn	Lys
				100					105					110		

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Met Val His Lys Pro Ser Gly Gln Ile Met Ala Val Lys Arg Ile Arg
 115 120 125
 Ser Thr Val Asp Glu Lys Glu Gln Lys Gln Leu Leu Met Asp Leu Asp
 130 135 140
 5 Val Val Met Arg Ser Ser Asp Cys Pro Tyr Ile Val Gln Phe Tyr Gly
 145 150 155 160
 Ala Leu Phe Arg Glu Gly Asp Cys Trp Ile Cys Met Glu Leu Met Ser
 165 170 175
 10 Thr Ser Phe Asp Lys Phe Tyr Lys Tyr Val Tyr Ser Val Leu Asp Asp
 180 185 190
 Val Ile Pro Glu Glu Ile Leu Gly Lys Ile Thr Leu Ala Thr Val Lys
 195 200 205
 Ala Leu Asn His Leu Lys Glu Asn Leu Lys Ile Ile His Arg Asp Ile
 210 215 220
 15 Lys Pro Ser Asn Ile Leu Leu Asp Arg Ser Gly Asn Ile Lys Leu Cys
 225 230 235 240
 Asp Phe Gly Ile Ser Gly Gln Leu Val Asp Ser Ile Ala Lys Thr Arg
 245 250 255
 20 Asp Ala Gly Cys Arg Pro Tyr Met Ala Pro Glu Arg Ile Asp Pro Ser
 260 265 270
 Ala Ser Arg Gln Gly Tyr Asp Val Arg Ser Asp Val Trp Ser Leu Gly
 275 280 285
 Ile Thr Leu Tyr Glu Leu Ala Thr Gly Arg Phe Pro Tyr Pro Lys Trp
 290 295 300
 25 Asn Ser Val Phe Asp Gln Leu Thr Gln Val Val Lys Gly Asp Pro Pro
 305 310 315 320
 Gln Leu Ser Asn Ser Glu Glu Arg Glu Phe Ser Pro Ser Phe Ile Asn
 325 330 335
 30 Phe Val Asn Leu Cys Leu Thr Lys Asp Glu Ser Lys Arg Pro Lys Tyr
 340 345 350
 Lys Glu Leu Leu Lys His Pro Phe Ile Leu Met Tyr Glu Glu Arg Ala
 355 360 365
 Val Glu Val Ala Cys Tyr Val Cys Lys Ile Leu Asp Gln Met Pro Ala
 370 375 380
 35 Thr Pro Ser Ser Pro Met Tyr Val Asp
 385 390

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3576 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 10...1206

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CTCCCAACA ATG GCG GCT CCG AGC CCG AGC GGC GGC GGC GGC TCC GGG GGC 51
 Met Ala Ala Pro Ser Pro Ser Gly Gly Gly Gly Ser Gly Gly
 1 5 10
 GGC AGC GGC AGC GGC ACC CCC GGC CCC GTA GGG TCC CCG GCG CCA GGC 99
 Gly Ser Gly Ser Gly Thr Pro Gly Pro Val Gly Ser Pro Ala Pro Gly
 15 20 25 30
 CAC CCG GCC GTC AGC AGC ATG CAG GGT AAA CGC AAA GCA CTG AAG TTG 147
 His Pro Ala Val Ser Ser Met Gln Gly Lys Arg Lys Ala Leu Lys Leu
 35 40 45

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	AAT	TTT	GCA	AAT	CCA	CCT	TTC	AAA	TCT	ACA	GCA	AGG	TTT	ACT	CTG	AAT	195
	Asn	Phe	Ala	Asn	Pro	Pro	Phe	Lys	Ser	Thr	Ala	Arg	Phe	Thr	Leu	Asn	
				50					55					60			
5	CCC	AAT	CCT	ACA	GGA	GTT	CAA	AAC	CCA	CAC	ATA	GAG	AGA	CTG	AGA	ACA	243
	Pro	Asn	Pro	Thr	Gly	Val	Gln	Asn	Pro	His	Ile	Glu	Arg	Leu	Arg	Thr	
			65					70					75				
	CAC	AGC	ATT	GAG	TCA	TCA	GGA	AAA	CTG	AAG	ATC	TCC	CCT	GAA	CAA	CAC	291
	His	Ser	Ile	Glu	Ser	Ser	Gly	Lys	Leu	Lys	Ile	Ser	Pro	Glu	Gln	His	
		80					85					90					
10	TGG	GAT	TTC	ACT	GCA	GAG	GAC	TTG	AAA	GAC	CTT	GGA	GAA	ATT	GGA	CGA	339
	Trp	Asp	Phe	Thr	Ala	Glu	Asp	Leu	Lys	Asp	Leu	Gly	Glu	Ile	Gly	Arg	
	95					100					105					110	
15	GGA	GCT	TAT	GGT	TCT	GTC	AAC	AAA	ATG	GTC	CAC	AAA	CCA	AGT	GGG	CAA	387
	Gly	Ala	Tyr	Gly	Ser	Val	Asn	Lys	Met	Val	His	Lys	Pro	Ser	Gly	Gln	
				115						120					125		
	ATA	ATG	GCA	GTT	AAA	AGA	ATT	CGG	TCA	ACA	GTG	GAT	GAA	AAA	GAA	CAA	435
	Ile	Met	Ala	Val	Lys	Arg	Ile	Arg	Ser	Thr	Val	Asp	Glu	Lys	Glu	Gln	
				130					135					140			
20	AAA	CAA	CTT	CTT	ATG	GAT	TTG	GAT	GTA	GTA	ATG	CGG	AGT	AGT	GAT	TGC	483
	Lys	Gln	Leu	Leu	Met	Asp	Leu	Asp	Val	Val	Met	Arg	Ser	Ser	Asp	Cys	
			145					150					155				
	CCA	TAC	ATT	GTT	CAG	TTT	TAT	GGT	GCA	CTC	TTC	AGA	GAG	GGT	GAC	TGT	531
	Pro	Tyr	Ile	Val	Gln	Phe	Tyr	Gly	Ala	Leu	Phe	Arg	Glu	Gly	Asp	Cys	
		160					165					170					
25	TGG	ATC	TGT	ATG	GAA	CTC	ATG	TCT	ACC	TCG	TTT	GAT	AAG	TTT	TAC	AAA	579
	Trp	Ile	Cys	Met	Glu	Leu	Met	Ser	Thr	Ser	Phe	Asp	Lys	Phe	Tyr	Lys	
	175					180					185					190	
30	TAT	GTA	TAT	AGT	GTA	TTA	GAT	GAT	GTT	ATT	CCA	GAA	GAA	ATT	TTA	GGC	627
	Tyr	Val	Tyr	Ser	Val	Leu	Asp	Asp	Val	Ile	Pro	Glu	Glu	Ile	Leu	Gly	
				195					200						205		
	AAA	ATC	ACT	TTA	GCA	ACT	GTG	AAA	GCA	CTA	AAC	CAC	TTA	AAA	GAA	AAC	675
	Lys	Ile	Thr	Leu	Ala	Thr	Val	Lys	Ala	Leu	Asn	His	Leu	Lys	Glu	Asn	
				210					215					220			
35	TTG	AAA	ATT	ATT	CAC	AGA	GAT	ATC	AAA	CCT	TCC	AAT	ATT	CTT	CTG	GAC	723
	Leu	Lys	Ile	Ile	His	Arg	Asp	Ile	Lys	Pro	Ser	Asn	Ile	Leu	Leu	Asp	
			225					230					235				
	AGA	AGT	GGA	AAT	ATT	AAG	CTC	TGT	GAC	TTC	GGC	ATC	AGT	GGA	CAG	CTT	771
	Arg	Ser	Gly	Asn	Ile	Lys	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	Gln	Leu	
		240					245					250					
40	GTG	GAC	TCT	ATT	GCC	AAG	ACA	AGA	GAT	GCT	GGC	TGT	AGG	CCA	TAC	ATG	819
	Val	Asp	Ser	Ile	Ala	Lys	Thr	Arg	Asp	Ala	Gly	Cys	Arg	Pro	Tyr	Met	
	255					260					265					270	
45	GCA	CCT	GAA	AGA	ATA	GAC	CCA	AGC	GCA	TCA	CGA	CAA	GGA	TAT	GAT	GTC	867
	Ala	Pro	Glu	Arg	Ile	Asp	Pro	Ser	Ala	Ser	Arg	Gln	Gly	Tyr	Asp	Val	
				275						280					285		
	CGC	TCT	GAT	GTC	TGG	AGT	TTG	GGG	ATC	ACA	TTG	TAT	GAG	TTG	GCC	ACA	915
	Arg	Ser	Asp	Val	Trp	Ser	Leu	Gly	Ile	Thr	Leu	Tyr	Glu	Leu	Ala	Thr	
				290				295						300			
50	GGC	CGA	TTT	CCT	TAT	CCA	AAG	TGG	AAT	AGT	GTA	TTT	GAT	CAA	CTA	ACA	963
	Gly	Arg	Phe	Pro	Tyr	Pro	Lys	Trp	Asn	Ser	Val	Phe	Asp	Gln	Leu	Thr	
			305					310					315				

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	CAA GTC GTG AAA GGA GAT CCT CCG CAG CTG AGT AAT TCT GAG GAA AGG	1011
	Gln Val Val Lys Gly Asp Pro Pro Gln Leu Ser Asn Ser Glu Glu Arg	
	320 325 330	
5	GAA TTC TCC CCG AGT TTC ATC AAC TTT GTC AAC TTG TGC CTT ACG AAG	1059
	Glu Phe Ser Pro Ser Phe Ile Asn Phe Val Leu Cys Leu Thr Lys	
	335 340 345 350	
	GAT GAA TCC AAA AGG CCA AAG TAT AAA GAG CTT CTG AAA CAT CCC TTT	1107
	Asp Glu Ser Lys Arg Pro Lys Tyr Lys Glu Leu Leu Lys His Pro Phe	
	355 360 365	
10	ATT TTG ATG TAT GAA GAA CGT GCC GTT GAG GTC GCA TGC TAT GTT TGT	1155
	Ile Leu Met Tyr Glu Glu Arg Ala Val Glu Val Ala Cys Tyr Val Cys	
	370 375 380	
	AAA ATC CTG GAT CAA ATG CCA GCT ACT CCC AGC TCT CCC ATG TAT GTC	1203
15	Lys Ile Leu Asp Gln Met Pro Ala Thr Pro Ser Ser Pro Met Tyr Val	
	385 390 395	
	GAT TGATATCGCT GCTACATCAG ACTCTAGAAA AAAGGGCTGA GAGGAAGCAA GACGTA	1262
	Asp	
20	AAGAATTTTC ATCCCGTATC ACAGTGTTTT TATTGCTCGC CCAGACACCA TGTGCAATAA	1322
	GATTGGTGTG CGTTTCCATC ATGTCTGTAT ACTCCTGTCA CCTAGAACGT GCATCCTTGT	1382
	AATACCTGAT TGATCACACA GTGTTAGTGC TGGTCAGAGA GACCTCATCC TGCTCTTTTG	1442
	TGATGAACAT ATTCATGAAA TGTGGAAGTC AGTACGATCA AGTTGTTGAC TGTGATTAGA	1502
	TCACATCTTA AATTCATTTT TAGACTCAAA ACCTGGAGAT GCAGCTACTG GAATGGTGTG	1562
	TTGTTCAGCT TCCAAATCCT GGAAGGACAC AGTGATGAAT GTACTATATC TGAACATAGA	1622
25	AACCTCGGGCT TGAGTGAGAA GAGCTTGCAC AGCCAACGAG ACACATTGCC TTCTGGAGCT	1682
	GGGAGACAAA GGAGGAATTT ACTTTCTTCA CCAAGTGCAA TAGATTACTG ATGTGATATT	1742
	CTGTTGCTTT ACAGTTACAG TTGATGTTTG GGGATCGATG TGCTCAGCCA AATTTCTCTG	1802
	TTGAAATATC ATGTTAAATC AGAATGAAT TATCTTTACC AAAAACCATG TTGCGTTCAA	1862
	AGAGGTGAAC ATTAATAATAT AGAGACAGGA CAGAATGTGT TCTTTTCTCC TCTACCAGTC	1922
	CTATTTTTCAT ATGGGAAGAC TCAGGAGTCT GCCACTTGTC AAAGAAGGTG CTGATCCTAA	1982
30	GAATTTTTCAT TTCTCAGAAAT TCGGTGTGCT GCCAACTTGA TGTTCCACCT GCCACAAACC	2042
	ACCAGGACTG AAAGAAGAAA ACAGTACAGA AGGCAAAGTT TACAGATGTT TTTAATTCTA	2102
	GTATTTTATC TGGAAACAAT TGTAGCAGCT ATATATTTCC CCTTGGTCCC AAGCCTGATA	2162
	CTTTAGCCAT CATAACTCAC TAACAGGGAG AAGTAGCTAG TAGCAATGTG CTTTGATTGA	2222
	TTAGATAAAG ATTTCTAGTA GGCAGCAAAA GACCAAATCT CAGTTGTTTG CTTCTTGCCA	2282
35	TCACTGGTCC AGGTCTTCAG TTTCGGAATC TCTTTCCCTT CCCCTGTGGT CTATTGTGCG	2342
	TATGTGACTT GCGCTTAATC CAATATTTTG CCTTTTCTTCT ATATCAAAAA ACCTTTACAG	2402
	TTAGCAGGGA GTTTCCTTAC CGAGGATTTT TAACCCCCAA TCTCTCATAA TCGCTAGTGT	2462
	TTAAAAGGCT AAGAATAGTG GGGCCCCAACC GATGTGGTAG GTGATAAAGA GGCATCTTTT	2522
	CTAGAGACAC ATTGGACCAG ATGAGGATCC GAAACGGCAG CCTTTACGTT CATCACCTGC	2582
40	TAGAACCTCT CGTAGTCCAT CACCATTTCT TGGCATTGGA ATTCTACTGG AAAAAAATAC	2642
	AAAAAGCAAA ACAAACCCT CAGCACTGTT ACAAGAGGCC ATTTAAGTAT CTTGTGCTTC	2702
	TTCACCTACC CATTAGCCAG GTTCTCATTA GGTTTTGCTT GGGCCTCCCT GGCCTGAAC	2762
	CTTAGGCTTT GTATGACAGT GAAGCAGCAC TGTGAGTGGT TCAAGCACAC TGGAATATAA	2822
	AACAGTCATG GCCTGAGATG CAGGTGATGC CATTACAGAA CCAAATCGTG GCACGTATTG	2882
45	CTGTGTCTCC TCTCAGAGTG ACAGTCATAA ATACTGTCAA ACAATAAAGG GAGAATGGTG	2942
	CTGTTTAAAG TCACATCCCT GTAAATTGCA GAATTCAAAA GTGATTATCT CTTTGATCTA	3002
	CTTGCCCTCAT TTCCCTATCT TCTCCCCCAC GGTATCCTAA ACTTTAGACT TCCCCTGTT	3062
	CTGAAAGGAG ACATTGCTCT ATGTCTGCCT TCGACCACAG CAAGCCATCA TCCTCCATTG	3122
	CTCCCGGGGA CTCAAGAGGA ATCTGTTTCT CTGCTGTCAA CTTCCCATCT GGCTCAGCAT	3182
50	AGGGTCACTT TGCCATTATG CAAATGGAGA TAAAAGCAAT TCTGGCTGTC CAGGAGCTAA	3242
	TCTGACCGTT CTATTGTGTG GATGACCACA TAAGAAGGCA ATTTTAGTGT ATTAATCATA	3302
	GATTATTATA AACTATAAAC TTAAGGGCAA GGAGTTTATT ACAATGTATC TTTATTAAAA	3362
	CAAAAGGGTG TATAGTGTTT ACAAACGTG AAAATAGTGT AAGAACTGTA CATTGTGAGC	3422
	TCTGGTTATT TTTCTCTTGT ACCATAGAAA AATGTATAAA AATTATCAAA AAGCTAATGT	3482
55	GCAGGGATAT TGCCTTATTT GTCTGTAAAA AATGGAGCTC AGTAACATAA CTGCTTCTTG	3542
	GAGCTTTGGA ATATTTTATC CTGTATTCTT GTTT	3576

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(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 399 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

10	Met	Ala	Ala	Pro	Ser	Pro	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser
	1				5				10					15		
	Gly	Ser	Gly	Thr	Pro	Gly	Pro	Val	Gly	Ser	Pro	Ala	Pro	Gly	His	Pro
			20					25					30			
	Ala	Val	Ser	Ser	Met	Gln	Gly	Lys	Arg	Lys	Ala	Leu	Lys	Leu	Asn	Phe
		35					40					45				
15	Ala	Asn	Pro	Pro	Phe	Lys	Ser	Thr	Ala	Arg	Phe	Thr	Leu	Asn	Pro	Asn
	50					55					60					
	Pro	Thr	Gly	Val	Gln	Asn	Pro	His	Ile	Glu	Arg	Leu	Arg	Thr	His	Ser
	65				70					75					80	
	Ile	Glu	Ser	Ser	Gly	Lys	Leu	Lys	Ile	Ser	Pro	Glu	Gln	His	Trp	Asp
20				85					90					95		
	Phe	Thr	Ala	Glu	Asp	Leu	Lys	Asp	Leu	Gly	Glu	Ile	Gly	Arg	Gly	Ala
			100					105					110			
	Tyr	Gly	Ser	Val	Asn	Lys	Met	Val	His	Lys	Pro	Ser	Gly	Gln	Ile	Met
		115				120						125				
25	Ala	Val	Lys	Arg	Ile	Arg	Ser	Thr	Val	Asp	Glu	Lys	Glu	Gln	Lys	Gln
	130					135					140					
	Leu	Leu	Met	Asp	Leu	Asp	Val	Val	Met	Arg	Ser	Ser	Asp	Cys	Pro	Tyr
	145				150					155					160	
	Ile	Val	Gln	Phe	Tyr	Gly	Ala	Leu	Phe	Arg	Glu	Gly	Asp	Cys	Trp	Ile
30				165				170						175		
	Cys	Met	Glu	Leu	Met	Ser	Thr	Ser	Phe	Asp	Lys	Phe	Tyr	Lys	Tyr	Val
		180						185					190			
	Tyr	Ser	Val	Leu	Asp	Asp	Val	Ile	Pro	Glu	Glu	Ile	Leu	Gly	Lys	Ile
		195				200						205				
35	Thr	Leu	Ala	Thr	Val	Lys	Ala	Leu	Asn	His	Leu	Lys	Glu	Asn	Leu	Lys
	210					215					220					
	Ile	Ile	His	Arg	Asp	Ile	Lys	Pro	Ser	Asn	Ile	Leu	Leu	Asp	Arg	Ser
	225				230						235				240	
	Gly	Asn	Ile	Lys	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	Gln	Leu	Val	Asp
40				245					250					255		
	Ser	Ile	Ala	Lys	Thr	Arg	Asp	Ala	Gly	Cys	Arg	Pro	Tyr	Met	Ala	Pro
		260						265					270			
	Glu	Arg	Ile	Asp	Pro	Ser	Ala	Ser	Arg	Gln	Gly	Tyr	Asp	Val	Arg	Ser
		275				280						285				
45	Asp	Val	Trp	Ser	Leu	Gly	Ile	Thr	Leu	Tyr	Glu	Leu	Ala	Thr	Gly	Arg
	290				295						300					
	Phe	Pro	Tyr	Pro	Lys	Trp	Asn	Ser	Val	Phe	Asp	Gln	Leu	Thr	Gln	Val
	305				310					315					320	
	Val	Lys	Gly	Asp	Pro	Pro	Gln	Leu	Ser	Asn	Ser	Glu	Glu	Arg	Glu	Phe
50				325					330					335		
	Ser	Pro	Ser	Phe	Ile	Asn	Phe	Val	Asn	Leu	Cys	Leu	Thr	Lys	Asp	Glu
		340						345					350			
	Ser	Lys	Arg	Pro	Lys	Tyr	Lys	Glu	Leu	Leu	Lys	His	Pro	Phe	Ile	Leu
		355				360						365				
55	Met	Tyr	Glu	Glu	Arg	Ala	Val	Glu	Val	Ala	Cys	Tyr	Val	Cys	Lys	Ile
	370					375					380					
	Leu	Asp	Gln	Met	Pro	Ala	Thr	Pro	Ser	Ser	Pro	Met	Tyr	Val	Asp	
	385				390						395					

(2) INFORMATION FOR SEO ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 393 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

	Met 1	Pro	Lys	Lys	Lys 5	Pro	Thr	Pro	Ile	Gln 10	Leu	Asn	Pro	Ala	Pro 15	Asp
10	Gly	Ser	Ala	Val 20	Asn	Gly	Thr	Ser	Ser 25	Ala	Glu	Thr	Asn	Leu 30	Glu	Ala
	Leu	Gln	Lys 35	Lys	Leu	Glu	Glu	Leu 40	Glu	Leu	Asp	Glu	Gln 45	Gln	Arg	Lys
	Arg	Leu 50	Glu	Ala	Phe	Leu	Thr 55	Gln	Lys	Gln	Lys	Val 60	Gly	Glu	Leu	Lys
15	Asp 65	Asp	Asp	Phe	Glu	Lys 70	Ile	Ser	Glu	Leu	Gly 75	Ala	Gly	Asn	Gly	Gly 80
	Val	Val	Phe	Lys	Val 85	Ser	His	Lys	Pro	Ser 90	Gly	Leu	Val	Met 95	Ala	Arg
20	Lys	Leu	Ile 100	His	Leu	Glu	Ile	Lys	Pro 105	Ala	Ile	Arg	Asn 110	Gln	Ile	Ile
	Arg	Glu	Leu 115	Gln	Val	Leu	His	Glu 120	Cys	Asn	Ser	Pro	Tyr 125	Ile	Val	Gly
	Phe	Tyr 130	Gly	Ala	Phe	Tyr	Ser 135	Asp	Gly	Glu	Ile	Ser 140	Ile	Cys	Met	Glu
25	His 145	Met	Asp	Gly	Gly	Ser 150	Leu	Asp	Gln	Val	Leu 155	Lys	Lys	Ala	Gly	Arg 160
	Ile	Pro	Glu	Gln 165	Ile	Leu	Gly	Lys	Val	Ser 170	Ile	Ala	Val	Ile 175	Lys	Gly
30	Leu	Thr	Tyr 180	Leu	Arg	Glu	Lys	His 185	Lys	Ile	Met	His	Arg 190	Asp	Val	Lys
	Pro	Ser	Asn 195	Ile	Leu	Val	Asn	Ser 200	Arg	Gly	Glu	Ile	Lys 205	Leu	Cys	Asp
	Phe	Gly 210	Val	Ser	Gly	Gln	Leu 215	Ile	Asp	Ser	Met	Ala 220	Asn	Ser	Phe	Val
35	Gly 225	Thr	Arg	Ser	Tyr 230	Met	Ser	Pro	Glu	Arg	Leu 235	Gln	Gly	Thr	His	Tyr 240
	Ser	Val	Gln	Ser 245	Asp	Ile	Trp	Ser	Met	Gly 250	Leu	Ser	Leu	Val 255	Glu	Met
40	Ala	Val	Gly 260	Arg	Tyr	Pro	Ile	Pro 265	Pro	Pro	Asp	Ala	Lys 270	Glu	Leu	Glu
	Leu	Met	Phe 275	Gly	Cys	Gln	Val	Glu 280	Gly	Asp	Ala	Ala	Glu 285	Thr	Pro	Pro
	Arg	Pro 290	Arg	Thr	Pro	Gly	Arg 295	Pro	Leu	Ser	Ser	Tyr 300	Gly	Met	Asp	Ser
45	Arg 305	Pro	Pro	Met	Ala 310	Ile	Phe	Glu	Leu	Leu	Asp 315	Tyr	Ile	Val	Asn	Glu 320
	Pro	Pro	Pro	Lys 325	Leu	Pro	Ser	Gly	Val	Phe 330	Ser	Leu	Glu	Phe 335	Gln	Asp
50	Phe	Val	Asn 340	Lys	Cys	Leu	Ile	Lys 345	Asn	Pro	Ala	Glu	Arg 350	Ala	Asp	Leu
	Lys	Gln	Leu 355	Met	Val	His	Ala	Phe 360	Ile	Lys	Arg	Ser	Asp 365	Ala	Glu	Glu
	Val	Asp 370	Phe	Ala	Gly	Trp	Leu 375	Cys	Ser	Thr	Ile	Gly 380	Leu	Asn	Gln	Pro
55	Ser 385	Thr	Pro	Thr	His 390	Ala	Ala	Gly	Val							

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(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 400 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

	Met	Leu	Ala	Arg	Arg	Lys	Pro	Val	Leu	Pro	Ala	Leu	Thr	Ile	Asn	Pro
	1				5					10					15	
10	Thr	Ile	Ala	Glu	Gly	Pro	Ser	Pro	Thr	Ser	Glu	Gly	Ala	Ser	Glu	Ala
				20					25					30		
	Asn	Leu	Val	Asp	Leu	Gln	Lys	Lys	Leu	Glu	Glu	Leu	Glu	Leu	Asp	Glu
			35					40					45			
15	Gln	Gln	Lys	Lys	Arg	Leu	Glu	Ala	Phe	Leu	Thr	Gln	Lys	Ala	Lys	Val
		50					55					60				
	Gly	Glu	Leu	Lys	Asp	Asp	Phe	Glu	Arg	Ile	Ser	Glu	Leu	Gly	Ala	
	65					70				75					80	
	Gly	Asn	Gly	Gly	Val	Val	Thr	Lys	Val	Gln	His	Arg	Pro	Ser	Gly	Leu
					85					90					95	
20	Ile	Met	Ala	Arg	Lys	Leu	Ile	His	Leu	Glu	Ile	Lys	Pro	Ala	Ile	Arg
				100					105					110		
	Asn	Gln	Ile	Ile	Arg	Glu	Leu	Gln	Val	Leu	His	Glu	Cys	Asn	Ser	Pro
		115						120					125			
25	Tyr	Ile	Val	Gly	Phe	Tyr	Gly	Ala	Phe	Tyr	Ser	Asp	Gly	Glu	Ile	Ser
		130					135					140				
	Ile	Cys	Met	Glu	His	Met	Asp	Gly	Gly	Ser	Leu	Asp	Gln	Val	Leu	Lys
	145					150					155				160	
	Glu	Ala	Lys	Arg	Ile	Pro	Glu	Glu	Ile	Leu	Gly	Lys	Val	Ser	Ile	Ala
					165					170					175	
30	Val	Leu	Arg	Gly	Leu	Ala	Tyr	Leu	Arg	Glu	Lys	His	Gln	Ile	Met	His
				180					185					190		
	Arg	Asp	Val	Lys	Pro	Ser	Asn	Ile	Leu	Val	Asn	Ser	Arg	Gly	Glu	Ile
			195					200					205			
35	Lys	Leu	Cys	Asp	Phe	Gly	Val	Ser	Gly	Gln	Leu	Ile	Asp	Ser	Met	Ala
		210					215					220				
	Asn	Ser	Phe	Val	Gly	Thr	Arg	Ser	Tyr	Met	Ala	Pro	Glu	Arg	Leu	Gln
	225					230					235				240	
	Gly	Thr	His	Tyr	Ser	Val	Gln	Ser	Asp	Ile	Trp	Ser	Met	Gly	Leu	Ser
					245					250					255	
40	Leu	Val	Glu	Leu	Ala	Val	Gly	Arg	Tyr	Pro	Ile	Pro	Pro	Pro	Asp	Ala
				260					265					270		
	Lys	Glu	Leu	Glu	Ala	Ile	Phe	Gly	Arg	Pro	Val	Val	Asp	Gly	Glu	Glu
			275					280					285			
45	Gly	Glu	Pro	His	Ser	Ile	Ser	Pro	Arg	Pro	Arg	Pro	Pro	Gly	Arg	Pro
		290					295					300				
	Val	Ser	Gly	His	Gly	Met	Asp	Ser	Arg	Pro	Ala	Met	Ala	Ile	Phe	Glu
	305					310					315				320	
	Leu	Leu	Asp	Tyr	Ile	Val	Asn	Glu	Pro	Pro	Pro	Lys	Leu	Pro	Asn	Gly
					325					330					335	
50	Val	Phe	Thr	Pro	Asp	Phe	Gln	Glu	Phe	Val	Asn	Lys	Cys	Leu	Ile	Lys
				340					345					350		
	Asn	Pro	Ala	Glu	Arg	Ala	Asp	Leu	Lys	Met	Leu	Thr	Asn	His	Thr	Phe
			355					360					365			
55	Ile	Lys	Arg	Ser	Glu	Val	Glu	Glu	Val	Asp	Phe	Ala	Gly	Trp	Leu	Cys
		370					375					380				
	Lys	Thr	Leu	Arg	Leu	Asn	Gln	Pro	Gly	Thr	Pro	Thr	Arg	Thr	Ala	Val
	385					390					395					400

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 367 amino acids

19

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```

5   Gly Thr Thr Pro Arg Thr Gly Asn Ser Asn Asn Ser Asn Ser Gly Ser
    1      5      10      15
    Ser Gly Gly Gly Leu Phe Ala Asn Phe Ser Lys Tyr Val Asp Ile
      20      25      30
10  Lys Ser Gly Ser Leu Asn Phe Ala Gly Lys Leu Ser Leu Ser Ser Lys
    35      40      45
    Gly Ile Asp Phe Ser Asn Gly Ser Ser Ser Arg Ile Thr Leu Asp Glu
    50      55      60
    Leu Glu Phe Leu Asp Glu Leu Gly His Gly Asn Tyr Gly Asn Val Ser
    65      70      75      80
15  Lys Val Leu His Lys Pro Thr Asn Val Ile Met Ala Thr Lys Glu Val
    85      90      95
    Arg Leu Glu Leu Asp Glu Ala Lys Phe Arg Gln Ile Leu Met Glu Leu
    100     105     110
    Glu Val Leu His Lys Cys Asn Ser Pro Tyr Ile Val Asp Phe Tyr Gly
    115     120     125
20  Ala Phe Phe Ile Glu Gly Ala Val Tyr Met Cys Met Glu Tyr Met Asp
    130     135     140
    Gly Gly Ser Leu Asp Lys Ile Tyr Asp Glu Ser Ser Glu Ile Gly Gly
    145     150     155     160
25  Ile Asp Glu Pro Gln Leu Ala Phe Ile Ala Asn Ala Val Ile His Gly
    165     170     175
    Leu Lys Glu Leu Lys Glu Gln His Asn Ile Ile His Arg Asp Val Lys
    180     185     190
    Pro Thr Asn Ile Leu Cys Ser Ala Asn Gln Gly Thr Val Lys Leu Cys
    195     200     205
30  Asp Phe Gly Val Ser Gly Asn Leu Val Ala Ser Leu Ala Lys Thr Met
    210     215     220
    Asn Ile Gly Cys Gln Ser Tyr Met Ala Pro Glu Arg Ile Lys Ser Leu
    225     230     235     240
35  Asn Pro Asp Arg Ala Thr Tyr Thr Val Gln Ser Asp Ile Trp Ser Leu
    245     250     255
    Gly Leu Ser Ile Leu Glu Met Ala Leu Gly Arg Tyr Pro Tyr Pro Pro
    260     265     270
    Glu Thr Tyr Asp Asn Ile Phe Ser Gln Leu Ser Ala Ile Val Asp Gly
    275     280     285
40  Pro Pro Pro Arg Leu Pro Ser Asp Lys Phe Ser Ser Asp Ala Gln Asp
    290     295     300
    Phe Val Ser Leu Cys Leu Gln Lys Ile Pro Glu Arg Arg Pro Thr Tyr
    305     310     315     320
45  Ala Ala Leu Thr Glu His Pro Trp Leu Val Lys Tyr Arg Asn Gln Asp
    325     330     335
    Val His Met Ser Glu Tyr Ile Thr Glu Arg Leu Glu Arg Arg Asn Lys
    340     345     350
50  Ile Leu Arg Glu Arg Gly Glu Asn Gly Leu Ser Lys Asn Val Pro
    355     360     365

```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TTYTAYGGNG CNTTYTTYAT HGA

20

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

ATBCTYTCNG GNGCCATKTA

20

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Asp Tyr Lys Asp Asp Asp Asp Lys
 1 5

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1623 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 281...1318

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

30	GGAAAGGCAG CCTCCTGTAG GTGAAATTC TGTTCACTAC CTGGCCACCT GGCCTGACTG	60
	ACCTTCACAG CTTGATCATC TTCCTGAAGA GGCATTCAGG ATTCCCTCCA TCCCTACCCC	120
	TTCTGGACAA AGTCTTCCAC GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATACC	180
	CAGAGCCCTG CAACTCCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT CCTCAGAGAG	240
35	CTCCCCACAG CACCCTACAC CCCCCACCG GCCCGCCAC ATG CTG GGG CTC CCA	295
	Met Leu Gly Leu Pro	
	1 5	
	TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG	343
	Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln	
	10 15 20	
40	AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC	391
	Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly	
	25 30 35	
	CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG	439
45	Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met	
	40 45 50	

21

		GGC	AGT	GGT	ACC	TGT	GGT	CAG	GTG	TGG	AAG	ATG	CGG	TTC	CGG	AAG	ACA	487
		Gly	Ser	Gly	Thr	Cys	Gly	Gln	Val	Trp	Lys	Met	Arg	Phe	Arg	Lys	Thr	
			55					60					65					
5		GGC	CAC	ATC	ATT	GCT	GTT	AAG	CAA	ATG	CGG	CGC	TCT	GGG	AAC	AAG	GAA	535
		Gly	His	Ile	Ile	Ala	Val	Lys	Gln	Met	Arg	Arg	Ser	Gly	Asn	Lys	Glu	
			70				75					80					85	
		GAG	AAT	AAG	CGC	ATT	TTG	ATG	GAC	CTG	GAT	GTA	GTA	CTC	AAG	AGC	CAT	583
		Glu	Asn	Lys	Arg	Ile	Leu	Met	Asp	Leu	Asp	Val	Val	Leu	Lys	Ser	His	
						90					95					100		
10		GAC	TGC	CCT	TAC	ATC	GTT	CAG	TGC	TTT	GGC	ACC	TTC	ATC	ACC	AAC	ACA	631
		Asp	Cys	Pro	Tyr	Ile	Val	Gln	Cys	Phe	Gly	Thr	Phe	Ile	Thr	Asn	Thr	
					105					110					115			
		GAC	GTC	TTT	ATT	GCC	ATG	GAG	CTC	ATG	GGC	ACA	TGT	GCA	GAG	AAG	CTG	679
15		Asp	Val	Phe	Ile	Ala	Met	Glu	Leu	Met	Gly	Thr	Cys	Ala	Glu	Lys	Leu	
				120					125					130				
		AAG	AAA	CGA	ATG	CAG	GGC	CCC	ATT	CCA	GAG	CGA	ATC	CTG	GGC	AAC	ATG	727
		Lys	Lys	Arg	Met	Gln	Gly	Pro	Ile	Pro	Glu	Arg	Ile	Leu	Gly	Asn	Met	
			135					140					145					
20		ACT	GTG	GCG	ATT	GTG	AAA	GCA	CTG	TAC	TAT	CTG	AAG	GAG	AAG	CAT	GGC	775
		Thr	Val	Ala	Ile	Val	Lys	Ala	Leu	Tyr	Tyr	Leu	Lys	Glu	Lys	His	Gly	
			150				155					160					165	
		GTC	ATC	CAT	CGC	GAT	GTC	AAA	CCC	TCC	AAC	ATC	CTG	CTA	GAT	GAG	CGG	823
		Val	Ile	His	Arg	Asp	Val	Lys	Pro	Ser	Asn	Ile	Leu	Leu	Asp	Glu	Arg	
						170					175					180		
25		GGC	CAG	ATC	AAG	CTC	TGT	GAC	TTT	GGC	ATC	AGT	GGC	CGC	CTT	GTT	GAC	871
		Gly	Gln	Ile	Lys	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	Arg	Leu	Val	Asp	
					185					190					195			
		TCC	AAA	GCC	AAA	ACA	CGG	AGT	GCT	GGC	TGT	GCT	GCC	TAT	ATG	GCT	CCC	919
30		Ser	Lys	Ala	Lys	Thr	Arg	Ser	Ala	Gly	Cys	Ala	Ala	Tyr	Met	Ala	Pro	
				200					205					210				
		GAG	CGC	ATC	GAC	CCT	CCA	GAT	CCC	ACC	AAG	CCT	GAC	TAT	GAC	ATC	CGA	967
		Glu	Arg	Ile	Asp	Pro	Pro	Asp	Pro	Thr	Lys	Pro	Asp	Tyr	Asp	Ile	Arg	
			215					220					225					
35		GCT	GAT	GTG	TGG	AGC	CTG	GGC	ATC	TCA	CTG	GTG	GAG	CTG	GCA	ACA	GGA	1015
		Ala	Asp	Val	Trp	Ser	Leu	Gly	Ile	Ser	Leu	Val	Glu	Leu	Ala	Thr	Gly	
			230				235					240					245	
		CAG	TTC	CCC	TAT	AAG	AAC	TGC	AAG	ACG	GAC	TTT	GAG	GTC	CTC	ACC	AAA	1063
		Gln	Phe	Pro	Tyr	Lys	Asn	Cys	Lys	Thr	Asp	Phe	Glu	Val	Leu	Thr	Lys	
						250					255					260		
40		GTC	CTA	CAG	GAA	GAG	CCC	CCA	CTC	CTG	CCT	GGT	CAC	ATG	GGC	TTC	TCA	1111
		Val	Leu	Gln	Glu	Glu	Pro	Pro	Leu	Leu	Pro	Gly	His	Met	Gly	Phe	Ser	
					265					270					275			
		GGG	GAC	TTC	CAG	TCA	TTT	GTC	AAA	GAC	TGC	CTT	ACT	AAA	GAT	CAC	AGG	1159
45		Gly	Asp	Phe	Gln	Ser	Phe	Val	Lys	Asp	Cys	Leu	Thr	Lys	Asp	His	Arg	
				280					285					290				
		AAG	AGA	CCA	AAG	TAT	AAT	AAG	CTA	CTT	GAA	CAC	AGC	TTC	ATC	AAG	CAC	1207
		Lys	Arg	Pro	Lys	Tyr	Asn	Lys	Leu	Leu	Glu	His	Ser	Phe	Ile	Lys	His	
				295				300					305					
50		TAT	GAG	ATA	CTC	GAG	GTG	GAT	GTC	GCG	TCC	TGG	TTT	AAG	GAT	GTC	ATG	1255
		Tyr	Glu	Ile	Leu	Glu	Val	Asp	Val	Ala	Ser	Trp	Phe	Lys	Asp	Val	Met	
						315						320					325	

5 CTG CCC TTC TTC AGG TAGCCTCATG GCAGCGGCCA GCGCCGCAGG GGCCCCGGGC C 1359
Leu Pro Phe Phe Arg
345

	ACGGCCACCG	ACCCCCCCCC	CAACCTGGCC	AACCCAGCTG	CCCATCAGGG	GACCTGGGAC	1419
	CTGGACGACT	GCCAAGGACT	GAGGACAGAA	AGTAGGGGGT	TCCCATCCAG	CTCTGACTCC	1479
	CTGCCTACCA	GCTGTGGACA	AAAGGGCATG	CTGGTTCTTA	ATCCCTCCCC	CTCTGGGGTC	1539
10	AGCCACGAGT	GTGAGCCCCA	TCCCACCCCG	ACAGACACTG	TGAACGGAAG	ACAGCAGGCC	1599
	AAAAAAAAAA	AAAAAAAAAA	AAAA				1629

(i) SEOUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 346 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEO ID NO:18:

20	Met 1	Leu	Gly	Leu	Pro 5	Ser	Thr	Leu	Phe	Thr 10	Pro	Arg	Ser	Met	Glu 15	Ser
	Ile	Glu	Ile	Asp 20	Gln	Lys	Leu	Gln	Glu 25	Ile	Met	Lys	Gln	Thr 30	Gly	Tyr
25	Leu	Thr	Ile 35	Gly	Gly	Gln	Arg	Tyr 40	Gln	Ala	Glu	Ile	Asn 45	Asp	Leu	Glu
	Asn 50	Leu	Gly	Glu	Met	Gly	Ser 55	Gly	Thr	Cys	Gly	Gln 60	Val	Trp	Lys	Met
	Arg 65	Phe	Arg	Lys	Thr	Gly 70	His	Ile	Ile	Ala	Val 75	Lys	Gln	Met	Arg	Arg 80
30	Ser	Gly	Asn	Lys	Glu 85	Glu	Asn	Lys	Arg	Ile 90	Leu	Met	Asp	Leu	Asp 95	Val
	Val	Leu	Lys	Ser 100	His	Asp	Cys	Pro	Tyr 105	Ile	Val	Gln	Cys	Phe 110	Gly	Thr
	Phe	Ile	Thr 115	Asn	Thr	Asp	Val	Phe 120	Ile	Ala	Met	Glu	Leu 125	Met	Gly	Thr
35	Cys	Ala	Glu	Lys	Leu	Lys	Lys 135	Arg	Met	Gln	Gly	Pro 140	Ile	Pro	Glu	Arg
	Ile 145	Leu	Gly	Asn	Met	Thr 150	Val	Ala	Ile	Val	Lys 155	Ala	Leu	Tyr	Tyr	Leu 160
40	Lys	Glu	Lys	His	Gly 165	Val	Ile	His	Arg	Asp 170	Val	Lys	Pro	Ser	Asn 175	Ile
	Leu	Leu	Asp	Glu 180	Arg	Gly	Gln	Ile	Lys 185	Leu	Cys	Asp	Phe 190	Gly	Ile	Ser
	Gly	Arg	Leu 195	Val	Asp	Ser	Lys	Ala 200	Lys	Thr	Arg	Ser	Ala 205	Gly	Cys	Ala
45	Ala	Tyr	Met	Ala	Pro	Glu	Arg 215	Ile	Asp	Pro	Pro	Asp 220	Pro	Thr	Lys	Pro
	Asp 225	Tyr	Asp	Ile	Arg	Ala 230	Asp	Val	Trp	Ser	Leu 235	Gly	Ile	Ser	Leu 240	Val
50	Glu	Leu	Ala	Thr	Gly 245	Gln	Phe	Pro	Tyr	Lys 250	Asn	Cys	Lys	Thr	Asp 255	Phe
	Glu	Val	Leu	Thr 260	Lys	Val	Leu	Gln	Glu 265	Glu	Pro	Pro	Leu 270	Leu	Pro	Gly
	His	Met	Gly 275	Phe	Ser	Gly	Asp	Phe 280	Gln	Ser	Phe	Val 285	Lys	Asp	Cys	Leu
55	Thr	Lys	Asp	His	Arg	Lys	Arg 295	Pro	Lys	Tyr	Asn 300	Lys	Leu	Leu	Glu	His
	Ser 305	Phe	Ile	Lys	His	Tyr 310	Glu	Ile	Leu	Glu	Val 315	Asp	Val	Ala	Ser	Trp 320

23

Phe Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val
 325 330
 Leu Ser Gln His His Leu Pro Phe Phe Arg
 340 345

5 (2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1465 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 3...1169

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

	GC	ACG	AGC	CCT	GCT	CCT	GCC	CCG	TCC	CAG	CGA	GCA	GCC	CTG	CAA	CTC	47
	Thr	Ser	Pro	Ala	Pro	Ala	Pro	Ser	Gln	Arg	Ala	Ala	Leu	Gln	Leu		
	1				5					10					15		
20	CCA	CTG	GCC	AAC	GAT	GGG	GGC	AGC	CGC	TCA	CCA	TCC	TCA	GAG	AGC	TCC	95
	Pro	Leu	Ala	Asn	Asp	Gly	Gly	Ser	Arg	Ser	Pro	Ser	Ser	Glu	Ser	Ser	
				20					25					30			
	CCA	CAG	CAC	CCT	ACA	CCC	CCC	ACC	CGG	CCC	CGC	CAC	ATG	CTG	GGG	CTC	143
	Pro	Gln	His	Pro	Thr	Pro	Pro	Thr	Arg	Pro	Arg	His	Met	Leu	Gly	Leu	
				35					40					45			
25	CCA	TCA	ACC	TTG	TTC	ACA	CCG	CGC	AGT	ATG	GAG	AGC	ATC	GAG	ATT	GAC	191
	Pro	Ser	Thr	Leu	Phe	Thr	Pro	Arg	Ser	Met	Glu	Ser	Ile	Glu	Ile	Asp	
			50					55					60				
	CAG	AAG	CTG	CAG	GAG	ATC	ATG	AAG	CAG	ACA	GGG	TAC	CTG	ACT	ATC	GGG	239
30	Gln	Lys	Leu	Gln	Glu	Ile	Met	Lys	Gln	Thr	Gly	Tyr	Leu	Thr	Ile	Gly	
		65				70						75					
	GGC	CAG	CGT	TAT	CAG	GCA	GAA	ATC	AAT	GAC	TTG	GAG	AAC	TTG	GGT	GAG	287
	Gly	Gln	Arg	Tyr	Gln	Ala	Glu	Ile	Asn	Asp	Leu	Glu	Asn	Leu	Gly	Glu	
	80					85				90					95		
35	ATG	GGC	AGT	GGT	ACC	TGT	GGT	CAG	GTG	TGG	AAG	ATG	CGG	TTC	CGG	AAG	335
	Met	Gly	Ser	Gly	Thr	Cys	Gly	Gln	Val	Trp	Lys	Met	Arg	Phe	Arg	Lys	
				100						105					110		
	ACA	GGC	CAC	ATC	ATT	GCT	GTT	AAG	CAA	ATG	CGG	CGC	TCT	GGG	AAC	AAG	383
	Thr	Gly	His	Ile	Ile	Ala	Val	Lys	Gln	Met	Arg	Arg	Ser	Gly	Asn	Lys	
				115					120					125			
40	GAA	GAG	AAT	AAG	CGC	ATT	TTG	ATG	GAC	CTG	GAT	GTA	GTA	CTC	AAG	AGC	431
	Glu	Glu	Asn	Lys	Arg	Ile	Leu	Met	Asp	Leu	Asp	Val	Val	Leu	Lys	Ser	
			130					135					140				
	CAT	GAC	TGC	CCT	TAC	ATC	GTT	CAG	TGC	TTT	GGC	ACC	TTC	ATC	ACC	AAC	479
45	His	Asp	Cys	Pro	Tyr	Ile	Val	Gln	Cys	Phe	Gly	Thr	Phe	Ile	Thr	Asn	
		145				150						155					
	ACA	GAC	GTC	TTT	ATT	GCC	ATG	GAG	CTC	ATG	GGC	ACA	TGT	GCA	GAG	AAG	527
	Thr	Asp	Val	Phe	Ile	Ala	Met	Glu	Leu	Met	Gly	Thr	Cys	Ala	Glu	Lys	
	160					165					170					175	

24

	CTG AAG AAA CGA ATG CAG GGC CCC ATT CCA GAG CGA ATC CTG GGC AAG	575
	Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys	
	180 185 190	
5	ATG ACT GTG GCG ATT GTG AAA GCA CTG TAC TAT CTG AAG GAG AAG CAT	623
	Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His	
	195 200 205	
	GGC GTC ATC CAT CGC GAT GTC AAA CCC TCC AAC ATC CTG CTA GAT GAG	671
	Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu	
	210 215 220	
10	CGG GGC CAG ATC AAG CTC TGT GAC TTT GGC ATC AGT GGC CGC CTT GTT	719
	Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val	
	225 230 235	
	GAC TCC AAA GCC AAA ACA CGG AGT GCT GGC TGT GCT GCC TAT ATG GCT	767
15	Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala	
	240 245 250 255	
	CCC GAG CGC ATC GAC CCT CCA GAT CCC ACC AAG CCT GAC TAT GAC ATC	815
	Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile	
	260 265 270	
20	CGA GCT GAT GTG TGG AGC CTG GGC ATC TCA CTG GTG GAG CTG GCA ACA	863
	Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr	
	275 280 285	
	GGA CAG TTC CCC TAT AAG AAC TGC AAG ACG GAC TTT GAG GTC CTC ACC	911
	Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr	
	290 295 300	
25	AAA GTC CTA CAG GAA GAG CCC CCA CTC CTG CCT GGT CAC ATG GGC TTC	959
	Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe	
	305 310 315	
	TCA GGG GAC TTC CAG TCA TTT GTC AAA GAC TGC CTT ACT AAA GAT CAC	1007
30	Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His	
	320 325 330 335	
	AGG AAG AGA CCA AAG TAT AAT AAG CTA CTT GAA CAC AGC TTC ATC AAG	1055
	Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys	
	340 345 350	
35	CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT AAG GAT GTC	1103
	His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val	
	355 360 365	
	ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG AGT CAG CAC	1151
	Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His	
	370 375 380	
40	CAT CTG CCC TTC TTC AGG TAGCCTCATG GCAGCGGCCA GCGCCGAGG GGCCCCGG	1207
	His Leu Pro Phe Phe Arg	
	385	
45	GCCACGGCCA CCGACCCCCC CCCCACCTG GCCAACCCAG CTGCCCCATCA GGGGACCTGG	1267
	GACCTGGACG ACTGCCAAGG ACTGAGGACA GAAAGTAGGG GGTCCCCATC CAGCTCTGAC	1327
	TCCCTGCCTA CCAGCTGTGG ACAAAGGGC ATGCTGGTTC CTAATCCCTC CCACTCTGGG	1387
	GTCAGCCAGC AGTGTGAGCC CCATCCCACC CCGACAGACA CTGTGAACGG AAGACAGCAA	1447
	AAAAAAAAA AAAAAAA	1465

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 389 amino acids

50

25

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

	Thr	Ser	Pro	Ala	Pro	Ala	Pro	Ser	Gln	Arg	Ala	Ala	Leu	Gln	Leu	Pro
	1				5				10					15		
	Leu	Ala	Asn	Asp	Gly	Gly	Ser	Arg	Ser	Pro	Ser	Ser	Glu	Ser	Ser	Pro
			20					25					30			
10	Gln	His	Pro	Thr	Pro	Pro	Thr	Arg	Pro	Arg	His	Met	Leu	Gly	Leu	Pro
			35				40						45			
	Ser	Thr	Leu	Phe	Thr	Pro	Arg	Ser	Met	Glu	Ser	Ile	Glu	Ile	Asp	Gln
		50					55					60				
	Lys	Leu	Gln	Glu	Ile	Met	Lys	Gln	Thr	Gly	Tyr	Leu	Thr	Ile	Gly	Gly
15		65			70					75					80	
	Gln	Arg	Tyr	Gln	Ala	Glu	Ile	Asn	Asp	Leu	Glu	Asn	Leu	Gly	Glu	Met
					85				90					95		
	Gly	Ser	Gly	Thr	Cys	Gly	Gln	Val	Trp	Lys	Met	Arg	Phe	Arg	Lys	Thr
				100				105					110			
20	Gly	His	Ile	Ile	Ala	Val	Lys	Gln	Met	Arg	Arg	Ser	Gly	Asn	Lys	Glu
			115					120					125			
	Glu	Asn	Lys	Arg	Ile	Leu	Met	Asp	Leu	Asp	Val	Val	Leu	Lys	Ser	His
		130					135					140				
25	Asp	Cys	Pro	Tyr	Ile	Val	Gln	Cys	Phe	Gly	Thr	Phe	Ile	Thr	Asn	Thr
		145			150					155					160	
	Asp	Val	Phe	Ile	Ala	Met	Glu	Leu	Met	Gly	Thr	Cys	Ala	Glu	Lys	Leu
				165						170					175	
	Lys	Lys	Arg	Met	Gln	Gly	Pro	Ile	Pro	Glu	Arg	Ile	Leu	Gly	Lys	Met
				180				185						190		
30	Thr	Val	Ala	Ile	Val	Lys	Ala	Leu	Tyr	Tyr	Leu	Lys	Glu	Lys	His	Gly
			195					200					205			
	Val	Ile	His	Arg	Asp	Val	Lys	Pro	Ser	Asn	Ile	Leu	Leu	Asp	Glu	Arg
		210					215					220				
35	Gly	Gln	Ile	Lys	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	Arg	Leu	Val	Asp
		225			230						235				240	
	Ser	Lys	Ala	Lys	Thr	Arg	Ser	Ala	Gly	Cys	Ala	Ala	Tyr	Met	Ala	Pro
				245						250				255		
	Glu	Arg	Ile	Asp	Pro	Pro	Asp	Pro	Thr	Lys	Pro	Asp	Tyr	Asp	Ile	Arg
				260					265					270		
40	Ala	Asp	Val	Trp	Ser	Leu	Gly	Ile	Ser	Leu	Val	Glu	Leu	Ala	Thr	Gly
			275					280					285			
	Gln	Phe	Pro	Tyr	Lys	Asn	Cys	Lys	Thr	Asp	Phe	Glu	Val	Leu	Thr	Lys
		290					295					300				
45	Val	Leu	Gln	Glu	Glu	Pro	Pro	Leu	Leu	Pro	Gly	His	Met	Gly	Phe	Ser
		305				310					315				320	
	Gly	Asp	Phe	Gln	Ser	Phe	Val	Lys	Asp	Cys	Leu	Thr	Lys	Asp	His	Arg
				325						330				335		
	Lys	Arg	Pro	Lys	Tyr	Asn	Lys	Leu	Leu	Glu	His	Ser	Phe	Ile	Lys	His
				340					345					350		
50	Tyr	Glu	Ile	Leu	Glu	Val	Asp	Val	Ala	Ser	Trp	Phe	Lys	Asp	Val	Met
			355				360						365			
	Ala	Lys	Thr	Glu	Ser	Pro	Arg	Thr	Ser	Gly	Val	Leu	Ser	Gln	His	His
		370					375					380				
55	Leu	Pro	Phe	Phe	Arg											
	385															

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 393 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

60

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

	Ser	Ala	Ser	Ser	Ser	Ser	Ser	Ser	Ala	Ser	Ala	Phe	Ala	Ser	Ala	Ala
	1				5					10					15	
5	Pro	Ala	Thr	Gly	Thr	Phe	Gly	Gly	Thr	Tyr	Thr	Pro	Pro	Thr	Thr	Arg
				20					25					30		
	Val	Ser	Arg	Ala	Thr	Pro	Thr	Leu	Pro	Met	Leu	Ser	Ser	Gly	Pro	Gly
			35					40					45			
10	Gly	Gly	Leu	Asn	Arg	Thr	Arg	Pro	Asn	Ile	Leu	Pro	Leu	Pro	Thr	Pro
		50					55					60				
	Pro	His	Pro	Pro	Val	Ser	Glu	Thr	Asp	Met	Lys	Leu	Lys	Ile	Ile	Met
		65			70						75					80
	Glu	Gln	Thr	Gly	Lys	Leu	Asn	Ile	Asn	Gly	Arg	Gln	Tyr	Pro	Thr	Asp
					85					90					95	
15	Ile	Asn	Asp	Leu	Lys	His	Leu	Gly	Asp	Leu	Gly	Asn	Gly	Thr	Ser	Gly
				100					105					110		
	Asn	Val	Val	Lys	Met	Met	His	Leu	Ser	Ser	Asn	Thr	Ile	Ile	Ala	Val
			115					120					125			
20	Lys	Gln	Met	Arg	Arg	Thr	Gly	Asn	Ala	Glu	Glu	Asn	Lys	Arg	Ile	Leu
		130					135					140				
	Met	Asp	Leu	Asp	Val	Val	Leu	Lys	Ser	His	Asp	Cys	Lys	Tyr	Ile	Val
		145			150						155					160
	Lys	Cys	Leu	Gly	Cys	Phe	Val	Arg	Asp	Pro	Asp	Val	Trp	Ile	Cys	Met
					165					170					175	
25	Glu	Leu	Met	Ser	Met	Cys	Phe	Asp	Lys	Leu	Leu	Lys	Leu	Ser	Lys	Lys
				180					185					190		
	Pro	Val	Pro	Glu	Gln	Ile	Leu	Gly	Lys	Val	Thr	Val	Ala	Thr	Val	Asn
			195					200					205			
30	Ala	Leu	Ser	Tyr	Leu	Lys	Asp	Lys	His	Gly	Val	Ile	His	Arg	Asp	Val
		210					215					220				
	Lys	Pro	Ser	Asn	Ile	Leu	Ile	Asp	Glu	Arg	Gly	Asn	Ile	Lys	Leu	Cys
		225				230					235					240
	Asp	Phe	Gly	Ile	Ser	Gly	Arg	Leu	Val	Asp	Ser	Lys	Ala	Lys	Thr	Arg
				245						250					255	
35	Ser	Ala	Gly	Cys	Ala	Ala	Tyr	Met	Ala	Pro	Glu	Arg	Ile	Asp	Pro	Lys
				260					265					270		
	Lys	Pro	Lys	Tyr	Asp	Ile	Arg	Ala	Asp	Val	Trp	Ser	Leu	Gly	Ile	Thr
			275					280					285			
40	Leu	Val	Glu	Leu	Ala	Thr	Ala	Arg	Ser	Pro	Tyr	Glu	Gly	Cys	Asn	Thr
		290					295					300				
	Asp	Phe	Glu	Val	Leu	Thr	Lys	Val	Leu	Asp	Ser	Glu	Pro	Pro	Cys	Leu
					310					315						320
	Pro	Tyr	Gly	Glu	Gly	Tyr	Asn	Phe	Ser	Gln	Gln	Phe	Arg	Asp	Phe	Val
					325					330					335	
45	Ile	Lys	Cys	Leu	Thr	Lys	Asn	His	Gln	Asp	Arg	Pro	Lys	Tyr	Pro	Glu
				340					345					350		
	Leu	Leu	Ala	Gln	Pro	Phe	Ile	Arg	Ile	Tyr	Glu	Ser	Ala	Lys	Val	Asp
			355					360					365			
50	Val	Pro	Asn	Gln	Ser	Ile	Lys	Asp	Asn	Arg	Leu	Arg	Ala	Asn	Gly	Asp
		370					375					380				
	Pro	Thr	Leu	Gln	Arg	Leu	Pro	Asn	Ser							
						385										

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 405 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

	Ile	Gly	Gln	Val	Leu	Pro	Glu	Ala	Thr	Thr	Thr	Ala	Phe	Glu	Tyr	Glu
	1				5					10					15	
5	Asp	Glu	Asp	Gly	Asp	Arg	Ile	Thr	Val	Arg	Ser	Asp	Glu	Glu	Met	Lys
				20					25					30		
	Ala	Met	Leu	Ser	Tyr	Tyr	Tyr	Ser	Thr	Val	Met	Glu	Gln	Gln	Val	Asn
			35					40					45			
	Gly	Gln	Leu	Ile	Glu	Pro	Leu	Gln	Ile	Phe	Pro	Arg	Ala	Cys	Lys	Pro
		50					55					60				
10	Pro	Gly	Glu	Arg	Asn	Ile	His	Gly	Leu	Lys	Val	Asn	Thr	Arg	Ala	Gly
	65					70					75				80	
	Pro	Ser	Gln	His	Ser	Ser	Pro	Ala	Val	Ser	Asp	Ser	Leu	Pro	Ser	Asn
				85						90				95		
15	Ser	Leu	Lys	Lys	Ser	Ser	Ala	Glu	Leu	Lys	Lys	Ile	Leu	Ala	Asn	Gly
				100					105					110		
	Gln	Met	Asn	Glu	Gln	Asp	Ile	Arg	Tyr	Arg	Asp	Thr	Leu	Gly	His	Gly
			115					120					125			
	Asn	Gly	Gly	Thr	Val	Glu	Lys	Met	Arg	His	Val	Pro	Ser	Gly	Lys	Ile
		130					135					140				
20	Leu	Ala	Val	Lys	Val	Ile	Leu	Leu	Asp	Ile	Thr	Leu	Glu	Leu	Gln	Lys
	145					150					155				160	
	Gln	Ile	Met	Ser	Glu	Leu	Glu	Ile	Leu	Ile	Lys	Cys	Asp	Ser	Ser	Tyr
				165							170				175	
25	Ile	Ile	Gly	Phe	Tyr	Gly	Ala	Phe	Phe	Val	Glu	Asn	Arg	Ile	Ser	Ile
			180					185						190		
	Cys	Thr	Glu	Phe	Met	Asp	Gly	Gly	Ser	Leu	Asp	Asp	Ile	Gly	Lys	Met
		195					200					205				
	Pro	Glu	His	Val	Leu	Gly	Arg	Ile	Ala	Val	Ala	Val	Val	Lys	Gly	Leu
		210				215						220				
30	Thr	Tyr	Lys	Gly	Leu	Thr	Tyr	Leu	Trp	Ser	Leu	Lys	Ile	Leu	His	Arg
	225					230					235				240	
	Asp	Val	Lys	Pro	Ser	Asn	Met	Val	Asn	Thr	Arg	Gly	Gln	Val	Lys	Leu
				245						250				255		
35	Cys	Asp	Phe	Gly	Val	Ser	Thr	Gln	Leu	Val	Asn	Ser	Ile	Ala	Lys	Thr
			260					265						270		
	Tyr	Val	Gly	Thr	Asn	Ala	Tyr	Met	Ala	Pro	Glu	Arg	Ile	Ser	Gly	Glu
			275					280					285			
	Gln	Tyr	Gly	Ile	His	Ser	Asp	Val	Trp	Ser	Leu	Gly	Ile	Thr	Met	Ile
		290				295						300				
40	Glu	Leu	Ala	Thr	Gly	Arg	Phe	Pro	Tyr	Pro	Lys	Trp	Asn	Ser	Val	Leu
	305					310					315				320	
	Gln	Leu	Leu	Gln	Cys	Ile	Val	Asp	Glu	Asp	Ser	Pro	Val	Leu	Pro	Val
				325					330					335		
45	Gly	Glu	Phe	Ser	Glu	Pro	Phe	Val	His	Phe	Ile	Thr	Gln	Cys	Met	Arg
			340						345					350		
	Thr	Gln	Pro	Lys	Glu	Arg	Pro	Ala	Pro	Glu	Glu	Leu	Met	Gly	His	Pro
		355						360					365			
	Phe	Ile	Val	Gln	Phe	Asn	Asp	Gly	Asn	Ala	Ala	Val	Val	Ser	Met	Trp
		370				375						380				
50	Val	Cys	Arg	Ala	Leu	Glu	Glu	Arg	Arg	Thr	Ser	Arg	Gly	Pro	Arg	Glu
	385					390					395				400	
	Ala	Ala	Ala	Gly	His											
				405												

(2) INFORMATION FOR SEQ ID NO:23:

- 55 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 18 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- 60 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

ATNGCNGTNA ARCARATG

18

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ATNCKYTCNG GNGCCATRTA

20

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 843 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 62...841

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

	TGTTTGTCTG CCGGACTGAC GGGCGGCCGG GCGGTGCGCG GCGGCGGTGG CGGCGGGGAA	60
	G ATG GCG GCG TCC TCC CTG GAA CAG AAG CTG TCC CGC CTG GAA GCA AAG	109
25	Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys	
	1 5 10 15	
	CTG AAG CAG GAG AAC CGG GAG GCC CGG CGG AGG ATC GAC CTC AAC CTG	157
	Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu	
	20 25 30	
30	GAT ATC AGC CCC CAG CGG CCC AGG CCC ACC CTG CAG CTC CCG CTG GCC	205
	Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala	
	35 40 45	
	AAC GAT GGG GGC AGC CGC TCG CCA TCC TCA GAG AGC TCC CCG CAG CAC	253
35	Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His	
	50 55 60	
	CCC ACG CCC CCC GCC CGG CCC CGC CAC ATG CTG GGG CTC CCG TCA ACC	301
	Pro Thr Pro Pro Ala Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr	
	65 70 75 80	
40	CTG TTC ACA CCC CGC AGC ATG GAG AGC ATT GAG ATT GAC CAG AAG CTG	349
	Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu	
	85 90 95	
	CAG GAG ATC ATG AAG CAG ACG GGC TAC CTG ACC ATC GGG GGC CAG CGC	397
	Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg	
	100 105 110	
45	TAC CAG GCA GAA ATC AAC GAC CTG GAG AAC TTG GGC GAG ATG GGC AGC	445
	Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser	
	115 120 125	

29

	GGC ACC TGC GGC CAG GTG TGG AAG ATG CGC TTC CGG AAG ACC GGC CAC	493
	Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His	
	130 135 140	
5	GTC ATT GCC GTT AAG CAA ATG CGG CGC TCC GGG AAC AAG GAG GAG AAC	541
	Val Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn	
	145 150 155 160	
	AAG CGC ATC CTC ATG GAC CTG GAT GTG GTG CTG AAG AGC CAC GAC TGC	589
	Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys	
	165 170 175	
10	CCC TAC ATC GTG CAG TGC TTT GGG ACG TTC ATC ACC AAC ACG GAC GTC	637
	Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val	
	180 185 190	
15	TTC ATC GCC ATG GAG CTC ATG GGC ACC TGC GCT GAG AAG CTC AAG AAG	685
	Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys	
	195 200 205	
	CGG ATG CAG GGC CCC ATC CCC GAG CGC ATT CTG GGC AAG ATG ACA GTG	733
	Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val	
	210 215 220	
20	GCG ATT GTG AAG GCG CTG TAC TAC CTG AAG GAG AAG CAC GGT GTC ATC	781
	Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile	
	225 230 235 240	
	CAC CGC GAC GTC AAG CCC TCC AAC ATC CTG CTG GAC GAG CGG GGC CAG	829
	His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln	
	245 250 255	
25	ATC AAG CTG TGC GA	843
	Ile Lys Leu Cys	
	260	

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 260 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

	Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys	
	1 5 10 15	
	Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Ile Asp Leu Asn Leu	
	20 25 30	
40	Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala	
	35 40 45	
	Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His	
	50 55 60	
45	Pro Thr Pro Pro Ala Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr	
	65 70 75 80	
	Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu	
	85 90 95	
	Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg	
	100 105 110	
50	Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser	
	115 120 125	
	Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His	
	130 135 140	

30

Val Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn
 145 150 155 160
 Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys
 165 170 175
 5 Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val
 180 185 190
 Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys
 195 200 205
 10 Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val
 210 215 220
 Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile
 225 230 235 240
 His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln
 245 250 255
 15 Ile Lys Leu Cys
 260

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 1643 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

25

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 82...1338

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AGCGCAGGCG CAGTGCGGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG 60
 30 GCGGCAGCGG CGGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG 111
 Met Ala Ala Ser Ser Leu Glu Gln Lys Leu
 1 5 10
 TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG 159
 35 Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg
 15 20 25
 AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC 207
 Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr
 30 35 40
 40 CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA 255
 Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser
 45 50
 GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG 303
 Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met
 60 65 70
 45 CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC 351
 Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile
 75 80 85 90
 50 GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG 399
 Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu
 95 100 105
 ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC 447
 Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn
 110 115 120

	TTG	GGT	GAG	ATG	GGC	AGT	GGT	ACC	TGT	GGT	CAG	GTG	TGG	AAG	ATG	CGG	495
	Leu	Gly	Glu	Met	Gly	Ser	Gly	Thr	Cys	Gly	Gln	Val	Trp	Lys	Met	Arg	
			125					130					135				
5	TTC	CGG	AAG	ACA	GGC	CAC	ATC	ATT	GCT	GTT	AAG	CAA	ATG	CGG	CGC	TCT	543
	Phe	Arg	Lys	Thr	Gly	His	Ile	Ile	Ala	Val	Lys	Gln	Met	Arg	Arg	Ser	
		140					145					150					
	GGG	AAC	AAG	GAA	GAG	AAT	AAG	CGC	ATT	TTG	ATG	GAC	CTG	GAT	GTA	GTA	591
	Gly	Asn	Lys	Glu	Glu	Asn	Lys	Arg	Ile	Leu	Met	Asp	Leu	Asp	Val	Val	
	155					160					165					170	
10	CTC	AAG	AGC	CAT	GAC	TGC	CCT	TAC	ATC	GTT	CAG	TGC	TTT	GGC	ACC	TTC	639
	Leu	Lys	Ser	His	Asp	Cys	Pro	Tyr	Ile	Val	Gln	Cys	Phe	Gly	Thr	Phe	
					175					180					185		
	ATC	ACC	AAC	ACA	GAC	GTC	TTT	ATT	GCC	ATG	GAG	CTC	ATG	GGC	ACA	TGT	687
15	Ile	Thr	Asn	Thr	Asp	Val	Phe	Ile	Ala	Met	Glu	Leu	Met	Gly	Thr	Cys	
				190					195					200			
	GCA	GAG	AAG	CTG	AAG	AAA	CGA	ATG	CAG	GGC	CCC	ATT	CCA	GAG	CGA	ATC	735
	Ala	Glu	Lys	Leu	Lys	Lys	Arg	Met	Gln	Gly	Pro	Ile	Pro	Glu	Arg	Ile	
			205					210					215				
20	CTG	GGC	AAG	ATG	ACT	GTG	GCG	ATT	GTG	AAA	GCA	CTG	TAC	TAT	CTG	AAG	783
	Leu	Gly	Lys	Met	Thr	Val	Ala	Ile	Val	Lys	Ala	Leu	Tyr	Tyr	Leu	Lys	
		220					225					230					
	GAG	AAG	CAT	GGC	GTC	ATC	CAT	CGC	GAT	GTC	AAA	CCC	TCC	AAC	ATC	CTG	831
	Glu	Lys	His	Gly	Val	Ile	His	Arg	Asp	Val	Lys	Pro	Ser	Asn	Ile	Leu	
	235					240					245					250	
25	CTA	GAT	GAG	CGG	GGC	CAG	ATC	AAG	CTC	TGT	GAC	TTT	GGC	ATC	AGT	GGC	879
	Leu	Asp	Glu	Arg	Gly	Gln	Ile	Lys	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	
					255					260					265		
	CGC	CTT	GTT	GAC	TCC	AAA	GCC	AAA	ACA	CGG	AGT	GCT	GGC	TGT	GCT	GCC	927
30	Arg	Leu	Val	Asp	Ser	Lys	Ala	Lys	Thr	Arg	Ser	Ala	Gly	Cys	Ala	Ala	
				270					275					280			
	TAT	ATG	GCT	CCC	GAG	CGC	ATC	GAC	CCT	CCA	GAT	CCC	ACC	AAG	CCT	GAC	975
	Tyr	Met	Ala	Pro	Glu	Arg	Ile	Asp	Pro	Pro	Asp	Pro	Thr	Lys	Pro	Asp	
			285					290					295				
35	TAT	GAC	ATC	CGA	GCT	GAT	GTG	TGG	AGC	CTG	GGC	ATC	TCA	CTG	GTG	GAG	1023
	Tyr	Asp	Ile	Arg	Ala	Asp	Val	Trp	Ser	Leu	Gly	Ile	Ser	Leu	Val	Glu	
		300					305					310					
	CTG	GCA	ACA	GGA	CAG	TTC	CCC	TAT	AAG	AAC	TGC	AAG	ACG	GAC	TTT	GAG	1071
	Leu	Ala	Thr	Gly	Gln	Phe	Pro	Tyr	Lys	Asn	Cys	Lys	Thr	Asp	Phe	Glu	
	315					320					325					330	
40	GTC	CTC	ACC	AAA	GTC	CTA	CAG	GAA	GAG	CCC	CCA	CTC	CTG	CCT	GGT	CAC	1119
	Val	Leu	Thr	Lys	Val	Leu	Gln	Glu	Glu	Pro	Pro	Leu	Leu	Pro	Gly	His	
					335					340					345		
	ATG	GGC	TTC	TCA	GGG	GAC	TTC	CAG	TCA	TTT	GTC	AAA	GAC	TGC	CTT	ACT	1167
45	Met	Gly	Phe	Ser	Gly	Asp	Phe	Gln	Ser	Phe	Val	Lys	Asp	Cys	Leu	Thr	
				350				355						360			
	AAA	GAT	CAC	AGG	AAG	AGA	CCA	AAG	TAT	AAT	AAG	CTA	CTT	GAA	CAC	AGC	1215
	Lys	Asp	His	Arg	Lys	Arg	Pro	Lys	Tyr	Asn	Lys	Leu	Leu	Glu	His	Ser	
			365					370					375				

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	TTC ATC AAG CAC TAT GAG ATA CTC GAG GTG GAT GTC GCG TCC TGG TTT	1263
	Phe Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe	
	380 385 390	
5	AAG GAT GTC ATG GCG AAG ACC GAG TCC CCA AGG ACT AGT GGA GTC CTG	1311
	Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu	
	395 400 405 410	
	AGT CAG CAC CAT CTG CCC TTC TTC AGG TAGCCTCATG GCAGCGGCCA GCCCCGC	1365
	Ser Gln His His Leu Pro Phe Phe Arg	
	415	
10	AGGGGCCCCG GGCCACGGCC ACCGACCCCC CCCCCAACCT GGCCAACCCA GCTGCCCATC	1425
	AGGGGACCTG GGACCTGGAC GACTGCCAAG GACTGAGGAC AGAAAGTAGG GGGTTCCTCAT	1485
	CCAGCTCTGA CTCCTGCCT ACCAGCTGTG GACAAAAGGG CATGCTGGTT CCTAATCCCT	1545
	CCCACTCTGG GGTCAGCCAG CAGTGTGAGC CCCATCCCAC CCCGACAGAC ACTGTGAACG	1605
	GAAGACAGCA GGCCAAAAA AAAAAAAAAA AAAAAAAA	1643
15	(2) INFORMATION FOR SEQ ID NO:28:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 419 amino acids	
	(B) TYPE: amino acid	
	(D) TOPOLOGY: linear	
20	(ii) MOLECULE TYPE: protein	
	(v) FRAGMENT TYPE: internal	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:	
	Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys	
	1 5 10 15	
25	Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Arg Ile Asp Leu Asn Leu	
	20 25 30	
	Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala	
	35 40 45	
30	Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser Pro Gln His	
	50 55 60	
	Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr	
	65 70 75 80	
	Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu	
	85 90 95	
35	Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg	
	100 105 110	
	Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser	
	115 120 125	
40	Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His	
	130 135 140	
	Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn	
	145 150 155 160	
	Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys	
	165 170 175	
45	Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val	
	180 185 190	
	Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys	
	195 200 205	
50	Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val	
	210 215 220	
	Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile	
	225 230 235 240	
	His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln	
	245 250 255	
55	Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp Ser Lys	
	260 265 270	
	Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro Glu Arg	
	275 280 285	

33

Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg Ala Asp
 290 295 300
 Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly Gln Phe
 305 310 315 320
 5 Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys Val Leu
 325 330 335
 Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser Gly Asp
 340 345 350
 10 Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg Lys Arg
 355 360 365
 Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Lys His Tyr Glu
 370 375 380
 Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met Ala Lys
 385 390 395 400
 15 Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His Leu Pro
 405 410 415
 Phe Phe Arg

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1578 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 281...1420

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GGAAAGGCAG CCTCCTGTAG GTGAAAATTC TGTTCACTAC CTGGCCACCT GGCCTGACTG 60
 ACCTTCACAG CTTGATCATC TTCCTGAAGA GGCATTCAGG ATTCCCTCCA TCCCTACCCC 120
 TTCTGGACAA AGTCTTCCAC GTTTCCTTCC TGGGAGTTTC TTCCAGGAAC TGGAGATAACC 180
 CAGAGCCCTG CAACTCCCAC TGGCCAACGA TGGGGGCAGC CGCTCACCAT CCTCAGAGAG 240
 CTCCCCACAG CACCCTACAC CCCCCACCG GCCCGCCAC ATG CTG GGG CTC CCA 295
 Met Leu Gly Leu Pro
 1 5
 TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC GAG ATT GAC CAG 343
 Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln
 10 15 20
 AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG ACT ATC GGG GGC 391
 Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly
 25 30 35
 CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC TTG GGT GAG ATG 439
 Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met
 40 45 50
 GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG TTC CGG AAG ACA 487
 Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr
 55 60 65
 GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT GGG AAC AAG GAA 535
 Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu
 70 75 80 85
 GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA CTC AAG AGC CAT 583
 Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His
 90 95 100

	GAC	TGC	CCT	TAC	ATC	GTT	CAG	TGC	TTT	GGC	ACC	TTC	ATC	ACC	AAC	ACA	631
	Asp	Cys	Pro	Tyr	Ile	Val	Gln	Cys	Phe	Gly	Thr	Phe	Ile	Thr	Asn	Thr	
				105					110					115			
5	GAC	GTC	TTT	ATT	GCC	ATG	GAG	CTC	ATG	GGC	ACA	TGT	GCA	GAG	AAG	CTG	679
	Asp	Val	Phe	Ile	Ala	Met	Glu	Leu	Met	Gly	Thr	Cys	Ala	Glu	Lys	Leu	
			120					125					130				
	AAG	AAA	CGA	ATG	CAG	GGC	CCC	ATT	CCA	GAG	CGA	ATC	CTG	GGC	AAG	ATG	727
	Lys	Lys	Arg	Met	Gln	Gly	Pro	Ile	Pro	Glu	Arg	Ile	Leu	Gly	Lys	Met	
			135				140					145					
10	ACT	GTG	GCG	ATT	GTG	AAA	GCA	CTG	TAC	TAT	CTG	AAG	GAG	AAG	CAT	GGC	775
	Thr	Val	Ala	Ile	Val	Lys	Ala	Leu	Tyr	Tyr	Leu	Lys	Glu	Lys	His	Gly	
	150					155					160					165	
	GTC	ATC	CAT	CGC	GAT	GTC	AAA	CCC	TCC	AAC	ATC	CTG	CTA	GAT	GAG	CGG	823
15	Val	Ile	His	Arg	Asp	Val	Lys	Pro	Ser	Asn	Ile	Leu	Leu	Asp	Glu	Arg	
					170					175					180		
	GGC	CAG	ATC	AAG	CTC	TGT	GAC	TTT	GGC	ATC	AGT	GGC	CGC	CTT	GTT	GAC	871
	Gly	Gln	Ile	Lys	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	Arg	Leu	Val	Asp	
				185					190					195			
20	TCC	AAA	GCC	AAA	ACA	CGG	AGT	GCT	GGC	TGT	GCT	GCC	TAT	ATG	GCT	CCC	919
	Ser	Lys	Ala	Lys	Thr	Arg	Ser	Ala	Gly	Cys	Ala	Ala	Tyr	Met	Ala	Pro	
			200					205					210				
	GAG	CGC	ATC	GAC	CCT	CCA	GAT	CCC	ACC	AAG	CCT	GAC	TAT	GAC	ATC	CGA	967
	Glu	Arg	Ile	Asp	Pro	Pro	Asp	Pro	Thr	Lys	Pro	Asp	Tyr	Asp	Ile	Arg	
			215				220					225					
25	GCT	GAT	GTG	TGG	AGC	CTG	GGC	ATC	TCA	CTG	GTG	GAG	CTG	GCA	ACA	GGA	1015
	Ala	Asp	Val	Trp	Ser	Leu	Gly	Ile	Ser	Leu	Val	Glu	Leu	Ala	Thr	Gly	
	230					235					240					245	
	CAG	TTC	CCC	TAT	AAG	AAC	TGC	AAG	ACG	GAC	TTT	GAG	GTC	CTC	ACC	AAA	1063
30	Gln	Phe	Pro	Tyr	Lys	Asn	Cys	Lys	Thr	Asp	Phe	Glu	Val	Leu	Thr	Lys	
					250					255					260		
	GTC	CTA	CAG	GAA	GAG	CCC	CCA	CTC	CTG	CCT	GGT	CAC	ATG	GGC	TTC	TCA	1111
	Val	Leu	Gln	Glu	Glu	Pro	Pro	Leu	Leu	Pro	Gly	His	Met	Gly	Phe	Ser	
				265					270					275			
35	GGG	GAC	TTC	CAG	TCA	TTT	GTC	AAA	GAC	TGC	CTT	ACT	AAA	GAT	CAC	AGG	1159
	Gly	Asp	Phe	Gln	Ser	Phe	Val	Lys	Asp	Cys	Leu	Thr	Lys	Asp	His	Arg	
			280					285					290				
	AAG	AGA	CCA	AAG	TAT	AAT	AAG	CTA	CTT	GAA	CAC	AGC	TTC	ATC	ATC	AAG	1207
	Lys	Arg	Pro	Lys	Tyr	Asn	Lys	Leu	Leu	Glu	His	Ser	Phe	Ile	Ile	Lys	
			295				300					305					
40	CAC	TAT	GAG	ATA	CTC	GAG	GTG	GAT	GTC	GCG	TCC	TGG	TTT	AAG	GAT	GTC	1255
	His	Tyr	Glu	Ile	Leu	Glu	Val	Asp	Val	Ala	Ser	Trp	Phe	Lys	Asp	Val	
	310					315					320					325	
	ATG	GCG	AAG	ACC	GAG	TCC	CCA	AGG	ACT	AGT	GGA	GTC	CTG	AGT	CAG	CAC	1303
45	Met	Ala	Lys	Thr	Glu	Ser	Pro	Arg	Thr	Ser	Gly	Val	Leu	Ser	Gln	His	
					330					335					340		
	CAT	CTG	CCC	TTC	TTC	AGT	GGG	AGT	CTG	GAG	GAG	TCT	CCC	ACT	TCC	CCA	1351
	His	Leu	Pro	Phe	Phe	Ser	Gly	Ser	Leu	Glu	Glu	Ser	Pro	Thr	Ser	Pro	
				345					350					355			
50	CCT	TCT	CCC	AAG	TCC	TTC	CCT	CTG	TCA	CCA	GCC	ATC	CCT	CAG	GCC	CAG	1399
	Pro	Ser	Pro	Lys	Ser	Phe	Pro	Leu	Ser	Pro	Ala	Ile	Pro	Gln	Ala	Gln	
			360					365					370				

35

GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG GTCCCACCCT CTGA 1454
 Ala Glu Trp Val Ser Gly Arg
 375 380

5 CCTCCTCCTC AGGCCACCAG TGTTGCCCTC TTCCCTTTTT AAAACAAAAT ACCCTTGTTT 1514
 GTAAATCCTT AGACGCTTGA GAATAAAACC CTTCCTTTTT CTTCGAAAA AAAAAAAAAA 1574
 AAAA 1578

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

10

- (A) LENGTH: 380 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

15 Met Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser
 1 5 10 15
 Ile Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr
 20 20 25 30
 Leu Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu
 35 40 45
 Asn Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met
 50 55 60
 Arg Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg
 65 70 75 80
 25 Ser Gly Asn Lys Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val
 85 90 95
 Val Leu Lys Ser His Asp Cys Pro Tyr Ile Val Gln Cys Phe Gly Thr
 100 105 110
 30 Phe Ile Thr Asn Thr Asp Val Phe Ile Ala Met Glu Leu Met Gly Thr
 115 120 125
 Cys Ala Glu Lys Leu Lys Lys Arg Met Gln Gly Pro Ile Pro Glu Arg
 130 135 140
 Ile Leu Gly Lys Met Thr Val Ala Ile Val Lys Ala Leu Tyr Tyr Leu
 145 150 155 160
 35 Lys Glu Lys His Gly Val Ile His Arg Asp Val Lys Pro Ser Asn Ile
 165 170 175
 Leu Leu Asp Glu Arg Gly Gln Ile Lys Leu Cys Asp Phe Gly Ile Ser
 180 185 190
 40 Gly Arg Leu Val Asp Ser Lys Ala Lys Thr Arg Ser Ala Gly Cys Ala
 195 200 205
 Ala Tyr Met Ala Pro Glu Arg Ile Asp Pro Pro Asp Pro Thr Lys Pro
 210 215 220
 Asp Tyr Asp Ile Arg Ala Asp Val Trp Ser Leu Gly Ile Ser Leu Val
 225 230 235 240
 45 Glu Leu Ala Thr Gly Gln Phe Pro Tyr Lys Asn Cys Lys Thr Asp Phe
 245 250 255
 Glu Val Leu Thr Lys Val Leu Gln Glu Glu Pro Pro Leu Leu Pro Gly
 260 265 270
 50 His Met Gly Phe Ser Gly Asp Phe Gln Ser Phe Val Lys Asp Cys Leu
 275 280 285
 Thr Lys Asp His Arg Lys Arg Pro Lys Tyr Asn Lys Leu Leu Glu His
 290 295 300
 Ser Phe Ile Ile Lys His Tyr Glu Ile Leu Glu Val Asp Val Ala Ser
 305 310 315 320
 55 Trp Phe Lys Asp Val Met Ala Lys Thr Glu Ser Pro Arg Thr Ser Gly
 325 330 335
 Val Leu Ser Gln His His Leu Pro Phe Phe Ser Gly Ser Leu Glu Glu
 340 345 350

36

Ser Pro Thr Ser Pro Pro Ser Pro Lys Ser Phe Pro Leu Ser Pro Ala
 355 360 365
 Ile Pro Gln Ala Gln Ala Glu Trp Val Ser Gly Arg
 370 375 380

5 (2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1598 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
 (B) LOCATION: 82...1440

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

	AGCGCAGGCG CAGTGCAGTG TTTGTCTACC CCGGACTGAC GGGTGGCCTG GCGGTGAGCG	60
	GCGGCAGCGG CGGCGGGGAA G ATG GCG GCG TCC TCC CTG GAG CAG AAG CTG	111
	Met Ala Ala Ser Ser Leu Glu Gln Lys Leu	
	1 5 10	
20	TCC CGC CTG GAA GCC AAG CTG AAG CAG GAG AAC CGT GAG GCC CGC AGG	159
	Ser Arg Leu Glu Ala Lys Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg	
	15 20 25	
25	AGG ATC GAC CTC AAC TTG GAT ATC AGC CCA CAG CGG CCC AGG CCC ACC	207
	Arg Ile Asp Leu Asn Leu Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr	
	30 35 40	
	CTG CAA CTC CCA CTG GCC AAC GAT GGG GGC AGC CGC TCA CCA TCC TCA	255
	Leu Gln Leu Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser	
	45 50 55	
30	GAG AGC TCC CCA CAG CAC CCT ACA CCC CCC ACC CGG CCC CGC CAC ATG	303
	Glu Ser Ser Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His Met	
	60 65 70	
	CTG GGG CTC CCA TCA ACC TTG TTC ACA CCG CGC AGT ATG GAG AGC ATC	351
	Leu Gly Leu Pro Ser Thr Leu Phe Thr Pro Arg Ser Met Glu Ser Ile	
	75 80 85 90	
35	GAG ATT GAC CAG AAG CTG CAG GAG ATC ATG AAG CAG ACA GGG TAC CTG	399
	Glu Ile Asp Gln Lys Leu Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu	
	95 100 105	
40	ACT ATC GGG GGC CAG CGT TAT CAG GCA GAA ATC AAT GAC TTG GAG AAC	447
	Thr Ile Gly Gly Gln Arg Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn	
	110 115 120	
	TTG GGT GAG ATG GGC AGT GGT ACC TGT GGT CAG GTG TGG AAG ATG CGG	495
	Leu Gly Glu Met Gly Ser Gly Thr Cys Gly Gln Val Trp Lys Met Arg	
	125 130 135	
45	TTC CGG AAG ACA GGC CAC ATC ATT GCT GTT AAG CAA ATG CGG CGC TCT	543
	Phe Arg Lys Thr Gly His Ile Ile Ala Val Lys Gln Met Arg Arg Ser	
	140 145 150	
	GGG AAC AAG GAA GAG AAT AAG CGC ATT TTG ATG GAC CTG GAT GTA GTA	591
	Gly Asn Lys Glu Glu Asn Lys Arg Ile Leu Met Asp Leu Asp Val Val	
	155 160 165 170	

37

	CTC	AAG	AGC	CAT	GAC	TGC	CCT	TAC	ATC	GTT	CAG	TGC	TTT	GGC	ACC	TTC	639
	Leu	Lys	Ser	His	Asp	Cys	Pro	Tyr	Ile	Val	Gln	Cys	Phe	Gly	Thr	Phe	
					175					180					185		
5	ATC	ACC	AAC	ACA	GAC	GTC	TTT	ATT	GCC	ATG	GAG	CTC	ATG	GGC	ACA	TGT	687
	Ile	Thr	Asn	Thr	Asp	Val	Phe	Ile	Ala	Met	Glu	Leu	Met	Gly	Thr	Cys	
				190					195					200			
	GCA	GAG	AAG	CTG	AAG	AAA	CGA	ATG	CAG	GGC	CCC	ATT	CCA	GAG	CGA	ATC	735
	Ala	Glu	Lys	Leu	Lys	Lys	Arg	Met	Gln	Gly	Pro	Ile	Pro	Glu	Arg	Ile	
			205					210					215				
10	CTG	GGC	AAG	ATG	ACT	GTG	GCG	ATT	GTG	AAA	GCA	CTG	TAC	TAT	CTG	AAG	783
	Leu	Gly	Lys	Met	Thr	Val	Ala	Ile	Val	Lys	Ala	Leu	Tyr	Tyr	Leu	Lys	
		220					225					230					
	GAG	AAG	CAT	GGC	GTC	ATC	CAT	CGC	GAT	GTC	AAA	CCC	TCC	AAC	ATC	CTG	831
15	Glu	Lys	His	Gly	Val	Ile	His	Arg	Asp	Val	Lys	Pro	Ser	Asn	Ile	Leu	
	235				240					245						250	
	CTA	GAT	GAG	CGG	GGC	CAG	ATC	AAG	CTC	TGT	GAC	TTT	GGC	ATC	AGT	GGC	879
	Leu	Asp	Glu	Arg	Gly	Gln	Ile	Lys	Leu	Cys	Asp	Phe	Gly	Ile	Ser	Gly	
				255						260					265		
20	CGC	CTT	GTT	GAC	TCC	AAA	GCC	AAA	ACA	CGG	AGT	GCT	GGC	TGT	GCT	GCC	927
	Arg	Leu	Val	Asp	Ser	Lys	Ala	Lys	Thr	Arg	Ser	Ala	Gly	Cys	Ala	Ala	
				270					275					280			
	TAT	ATG	GCT	CCC	GAG	CGC	ATC	GAC	CCT	CCA	GAT	CCC	ACC	AAG	CCT	GAC	975
	Tyr	Met	Ala	Pro	Glu	Arg	Ile	Asp	Pro	Pro	Asp	Pro	Thr	Lys	Pro	Asp	
			285					290					295				
25	TAT	GAC	ATC	CGA	GCT	GAT	GTG	TGG	AGC	CTG	GGC	ATC	TCA	CTG	GTG	GAG	1023
	Tyr	Asp	Ile	Arg	Ala	Asp	Val	Trp	Ser	Leu	Gly	Ile	Ser	Leu	Val	Glu	
		300					305					310					
	CTG	GCA	ACA	GGA	CAG	TTC	CCC	TAT	AAG	AAC	TGC	AAG	ACG	GAC	TTT	GAG	1071
30	Leu	Ala	Thr	Gly	Gln	Phe	Pro	Tyr	Lys	Asn	Cys	Lys	Thr	Asp	Phe	Glu	
	315				320						325					330	
	GTC	CTC	ACC	AAA	GTC	CTA	CAG	GAA	GAG	CCC	CCA	CTC	CTG	CCT	GGT	CAC	1119
	Val	Leu	Thr	Lys	Val	Leu	Gln	Glu	Glu	Pro	Pro	Leu	Leu	Pro	Gly	His	
				335						340					345		
35	ATG	GGC	TTC	TCA	GGG	GAC	TTC	CAG	TCA	TTT	GTC	AAA	GAC	TGC	CTT	ACT	1167
	Met	Gly	Phe	Ser	Gly	Asp	Phe	Gln	Ser	Phe	Val	Lys	Asp	Cys	Leu	Thr	
				350				355						360			
	AAA	GAT	CAC	AGG	AAG	AGA	CCA	AAG	TAT	AAT	AAG	CTA	CTT	GAA	CAC	AGC	1215
	Lys	Asp	His	Arg	Lys	Arg	Pro	Lys	Tyr	Asn	Lys	Leu	Leu	Glu	His	Ser	
			365					370					375				
40	TTC	ATC	ATC	AAG	CAC	TAT	GAG	ATA	CTC	GAG	GTG	GAT	GTC	GCG	TCC	TGG	1263
	Phe	Ile	Ile	Lys	His	Tyr	Glu	Ile	Leu	Glu	Val	Asp	Val	Ala	Ser	Trp	
		380					385					390					
	TTT	AAG	GAT	GTC	ATG	GCG	AAG	ACC	GAG	TCC	CCA	AGG	ACT	AGT	GGA	GTC	1311
45	Phe	Lys	Asp	Val	Met	Ala	Lys	Thr	Glu	Ser	Pro	Arg	Thr	Ser	Gly	Val	
	395				400						405				410		
	CTG	AGT	CAG	CAC	CAT	CTG	CCC	TTC	TTC	AGT	GGG	AGT	CTG	GAG	GAG	TCT	1359
	Leu	Ser	Gln	His	His	Leu	Pro	Phe	Phe	Ser	Gly	Ser	Leu	Glu	Glu	Ser	
				415						420				425			
50	CCC	ACT	TCC	CCA	CCT	TCT	CCC	AAG	TCC	TTC	CCT	CTG	TCA	CCA	GCC	ATC	1407
	Pro	Thr	Ser	Pro	Pro	Ser	Pro	Lys	Ser	Phe	Pro	Leu	Ser	Pro	Ala	Ile	
				430					435					440			

38

CCT CAG GCC CAG GCA GAG TGG GTC TCG GGC AGG TAGGGACCTG GAGTGGCCTG 1460
 Pro Gln Ala Gln Ala Glu Trp Val Ser Gly Arg
 445 450

5 GTCCACCCCT CTGACCTCCT CCTCAGGCCA CCAGTGTTCCT TTTTAAAACA 1520
 AAATACCCTT GTTTGTAAAT CCTTAGACGC TTGAGAATAA AACCCCTCCC TTTTCTTCCG 1580
 AAAAAAAAAA AAAAAAAAA 1598

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 453 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

15 Met Ala Ala Ser Ser Leu Glu Gln Lys Leu Ser Arg Leu Glu Ala Lys
 1 5 10 15
 Leu Lys Gln Glu Asn Arg Glu Ala Arg Arg Ile Asp Leu Asn Leu
 20 20 25 30
 Asp Ile Ser Pro Gln Arg Pro Arg Pro Thr Leu Gln Leu Pro Leu Ala
 35 40 45
 Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Pro Gln His
 50 55 60
 Pro Thr Pro Pro Thr Arg Pro Arg His Met Leu Gly Leu Pro Ser Thr
 65 70 75 80
 25 Leu Phe Thr Pro Arg Ser Met Glu Ser Ile Glu Ile Asp Gln Lys Leu
 85 90 95
 Gln Glu Ile Met Lys Gln Thr Gly Tyr Leu Thr Ile Gly Gly Gln Arg
 100 105 110
 30 Tyr Gln Ala Glu Ile Asn Asp Leu Glu Asn Leu Gly Glu Met Gly Ser
 115 120 125
 Gly Thr Cys Gly Gln Val Trp Lys Met Arg Phe Arg Lys Thr Gly His
 130 135 140
 Ile Ile Ala Val Lys Gln Met Arg Arg Ser Gly Asn Lys Glu Glu Asn
 145 150 155 160
 35 Lys Arg Ile Leu Met Asp Leu Asp Val Val Leu Lys Ser His Asp Cys
 165 170 175
 Pro Tyr Ile Val Gln Cys Phe Gly Thr Phe Ile Thr Asn Thr Asp Val
 180 185 190
 Phe Ile Ala Met Glu Leu Met Gly Thr Cys Ala Glu Lys Leu Lys Lys
 195 200 205
 40 Arg Met Gln Gly Pro Ile Pro Glu Arg Ile Leu Gly Lys Met Thr Val
 210 215 220
 Ala Ile Val Lys Ala Leu Tyr Tyr Leu Lys Glu Lys His Gly Val Ile
 225 230 235 240
 45 His Arg Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg Gly Gln
 245 250 255
 Ile Lys Leu Cys Asp Phe Gly Ile Ser Gly Arg Leu Val Asp Ser Lys
 260 265 270
 Ala Lys Thr Arg Ser Ala Gly Cys Ala Ala Tyr Met Ala Pro Glu Arg
 275 280 285
 50 Ile Asp Pro Pro Asp Pro Thr Lys Pro Asp Tyr Asp Ile Arg Ala Asp
 290 295 300
 Val Trp Ser Leu Gly Ile Ser Leu Val Glu Leu Ala Thr Gly Gln Phe
 305 310 315 320
 55 Pro Tyr Lys Asn Cys Lys Thr Asp Phe Glu Val Leu Thr Lys Val Leu
 325 330 335
 Gln Glu Glu Pro Pro Leu Leu Pro Gly His Met Gly Phe Ser Gly Asp
 340 345 350

39

Phe Gln Ser Phe Val Lys Asp Cys Leu Thr Lys Asp His Arg Lys Arg
 355 360 365
 Pro Lys Tyr Asn Lys Leu Leu Glu His Ser Phe Ile Ile Lys His Tyr
 370 375 380
 5 Glu Ile Leu Glu Val Asp Val Ala Ser Trp Phe Lys Asp Val Met Ala
 385 390 395 400
 Lys Thr Glu Ser Pro Arg Thr Ser Gly Val Leu Ser Gln His His Leu
 405 410 415
 10 Pro Phe Phe Ser Gly Ser Leu Glu Glu Ser Pro Thr Ser Pro Pro Ser
 420 425 430
 Pro Lys Ser Phe Pro Leu Ser Pro Ala Ile Pro Gln Ala Gln Ala Glu
 435 440 445
 Trp Val Ser Gly Arg
 450

15 (2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 44 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Xaa Ser Pro Ala Pro Ala Pro Ser Gln Arg Ala Ala Leu Gln Leu
 1 5 10 15
 25 Pro Leu Ala Asn Asp Gly Gly Ser Arg Ser Pro Ser Ser Glu Ser Ser
 20 25 30
 Pro Gln His Pro Thr Pro Pro Thr Arg Pro Arg His
 35 40

(2) INFORMATION FOR SEQ ID NO:34:

30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 77 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

35 Glu Gly Gly Gly Val Lys His Met Ala Lys Leu Tyr Val Phe Tyr Gly
 1 5 10 15
 Ala Gly Cys Met Glu Met Ser Asp Ile Glu Leu Leu Leu His Arg Asp
 20 25 30
 40 Lys Pro Asn Leu Gly Lys Cys Asp Phe Gly Ser Gly Leu Ser Ala Gly
 35 40 45
 Tyr Met Pro Glu Arg Tyr Val Ser Asp Trp Ser Gly Glu Ala Arg Pro
 50 55 60
 Phe Leu Val Pro Leu Phe Phe Cys Leu Lys Arg Leu His
 65 70 75

45 328103.B11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14101

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 21/04

US CL :536/23.5; 435/183

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5; 435/4, 183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	CUENDA, A. et al., "Differential activation of stress-activated protein kinase kinases SKK4/MKK7 and SKK1/MKK4 by the mixed-lineage kinase-2 and mitogen-activated protein kinase(MKK) kinase-1," Biochemical Journal, 01 July 1998, Volume 333, part 1, pages 11-15; see entire document.	1,2, 10-12
A	MOODIE, S.A. et al., "Complexes of Ras-GTP with Raf-1 and Mitogen-Activated Protein Kinase Kinase," Science, 11 June 1993, volume 260, pages 1658-1661, see pages 1658-1659.	1, 2, 10-12

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

24 SEPTEMBER 1998

Date of mailing of the international search report

29 . 10 . 1998

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DENT, P. et al., "Activation of Mitogen-Activated Protein Kinase Kinase by v-Raf in NIH 3T3 Cells and in Vitro," Science, 04 September 1992, volume 257, pages 1404-1407, see pages 1404-1406.	1, 2
A	IRIE, K. et al., "MKK1 and MKK2, Which Encode Saccharomyces cervisiae Mitogen-Activated Protein Kinase-Kinase Homologs, Function in the Pathway Mediated by Protein Kinase C," Molecular and Cellular Biology, May 1993, Vol. 13, No. 5, pages 3076-3083, see pages 3076-3081.	1, 2
Y	TRAVERSE, S. et al., "Sustained activation of the mitogen-activated protein (MAP) kinase cascade may be required for differentiation of PC12 cells," Biochem. J. 1992, vol. 288, pages 351-355, see entire document.	1, 2
X, P	TOURNIER, C. et al., "Mitogen-activated protein kinase kinase 7 is an activator of the c-Jun NH(sub)2-terminal kinase," Proceedings of the National Academy of Sciences, July 1997, Vol. 94, pages 7337-7342; see entire document.	1, 2, 10-12
X, T	US 5,804,427 A (DAVIS et al.) 08 September 1998, see entire document.	1, 2, 10-12
A, P	US 5,753,446 A (JOHNSON) 19 May 1998, see entire document.	1, 2

INTERNATIONAL SEARCH REPORT

International application No.
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B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS; STN (file: Biosis, Registry)

Search Terms: mitogen activated protein kinase kinase; SEQ ID NO: 18, 20, 26, 28, 30, and 32

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1 and 2, drawn to mammalian mitogen-activated protein kinase kinase (MKK); and claims 10-12, drawn to method of measuring the activity of a mitogen-activated protein kinase kinase (MKK7).

Group II, claim(s) 3-5, drawn to isolated polynucleotide encoding MKK; claim 6, drawn to recombinant expression vector; and claim 7, drawn to a host cell.

Group III, claim(s) 8 and 9, drawn to purified antibodies; and claim 13, drawn to an immuno-based method for measuring the synthesis of MKK7.

Group IV, claim(s) 14, drawn to nucleic acid-based method for measuring the synthesis of MKK7.

Group V, claim(s) 15-17, drawn to a method for identifying a reagent that modulates MKK7 activity; claims 18 and 19, drawn to a method for identifying a reagent that modulates MKK7 synthesis; and claim 20, drawn to a nucleic acid-based method for identifying a reagent that modulates MKK7 expression.

Group VI, claim(s) 21-24, drawn to a method of treating a MKK7-mediated disorder.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The invention of Group I is drawn to an enzyme and a related method of use while the invention of Group II is drawn to a nucleic acid, a recombinant

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vector, and a life form- a host cell. Further, the invention of Group VI is drawn to a method of treating patients that may suffer from ischemic heart disease, kidney failure, oxidative liver damage, respiratory distress syndrome, heat radiation burns, etc., whereinsaid method requires the use of a drug. Said drug, however, is not the enzyme of Group I nor the nucleic acid, vector, or host cell of Group II. Further, the aspect of mitogen activated kinase kinase contributing to such diseases is known in the prior art. Accordingly, the claimed invnetions are not so inked by a special technical feature so to form a single inventive concept under PCT Rule 13.1.